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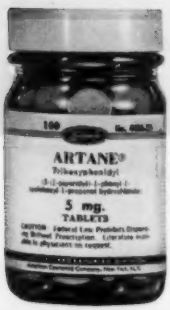

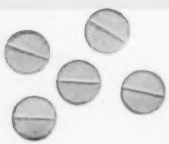

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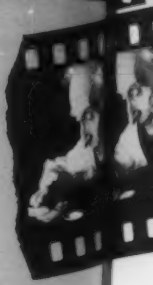
Parkinsonism



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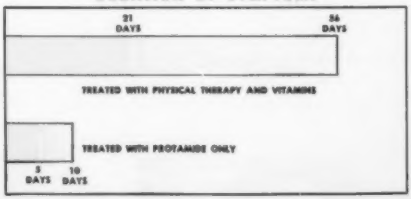

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NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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Neurology

Effects of Betatron Radiations on the Brain of Primates

Arthur Arnold, M.D., Percival Bailey, M.D. and John S. Laughlin, Ph.D.

FOR THE PAST FOUR YEARS studies have been in progress to determine and to analyze the effects of the newer sources of radiations on the normal brain of monkeys and on the tumors of the central nervous system of man. This report is concerned primarily with an analysis of the clinical and pathologic effects on the brain of the monkey of 23 mev. x-rays, as produced by the University of Illinois betatron. This study was also undertaken to gain some insight as to how the physical properties of high energy x-rays, as produced by the betatron, could be efficiently applied to the therapy of brain tumors.

PHYSICAL ASPECTS OF THE BETATRON

Physically, the betatron is a circular electron accelerator in which electrons (beta particles) are accelerated in a changing magnetic field, which is activated by a high frequency, alternating current. The electrons injected into the doughnut-shaped vacuum tube acquire enormous energies as a result of their induced acceleration. The energies acquired by the electrons are dependent upon the magnitude and the rate of change of the alternating magnetic field. Eventually, these highly "energized" electrons strike a small platinum target, in which x-rays of high energy are produced. The betatron can,

From the department of neurology and neurological surgery, Neuropsychiatric Institute, and the department of radiology, University of Illinois College of Medicine, Chicago.

This work was supported by grants from the U. S. Public Health Service and the Atomic Energy Commission.

therefore, be considered a source of x-rays of much higher energy than obtainable by conventional x-ray machines. The betatron can also produce separate high energy electron beams, which are being studied at present. The medical betatron of the University of Illinois has an energy of 23 mev. (million electron volts), which, when compared to the energies of 200–400 kev. (thousand electron volts) of the conventional x-ray machine, is approximately 100 times greater. This high energy potential of the betatron enables one to produce beams of x-rays which are, 1) free from any significant side-scatter, 2) more penetrating, and 3) more homogeneous than low energy x-ray beams. These features of the high energy x-ray beam employed in this study can best be seen in figure 1B.

This study was greatly facilitated by the precision radiation possible with our betatron. The uniformity of dose-distribution through the monkey brain, which we were able to obtain with the betatron x-ray beam, in the manner employed, cannot be duplicated with low energy x-ray sources. Hence, the betatron offers definite experimental advantages in the evaluation of the effects of x-rays upon tissues. Further comment upon these experimental advantages will be brought out under experimental procedures.

GENERAL OBSERVATIONS AND COMMENTS ON LITERATURE

Our findings to date, from these studies as well as other unreported studies, would indicate that the brain of both monkey and man is more radio-responsive than generally supposed and that the pathologic changes and clinical phenomena produced by these radiations appear to be due to a direct effect of the radiations upon the neural elements rather than to indirect effects resulting from vascular damage. These observations are contradictory to the conclusions drawn by previous investigators,[1–5] who have irradiated the central nervous system of a variety of animal species, including man.[6] In general, these authors concluded 1) that the central nervous system is highly radioresistant in that it requires many thousands of r to produce any recognizable pathologic or clinical effects, and 2) that any changes produced by the radiations are secondary to an interruption of the vascular bed, rather than to a direct injurious effect of the radiations upon the neural elements. An exception to the second concept was made by Davidoff and co-workers,[7] who exposed the brain and spinal cord of the adult monkey (Macacus rhesus) through an open wound to single doses of 200 kev. x-rays, from 1,000 to 5,000 r (as measured in air), and demonstrated that the nervous and glial cells were affected, whereas the changes in the blood vessels were surprisingly slight in degree. More recently Hicks and co-workers[8] indicated that the oligodendroglia could respond to x-rays, and Reynolds[9] found that the polarizing microscope was quite helpful in detecting changes in the white matter following irradiation. With reference to the brain of man, O'Connell and Brunschwig[10] and Wachowski and Chenault[11] noted in their patients receiving x-ray therapy that the radiation produced changes in all the neural elements and some of the vessels, but that the neural changes were primary effects rather than a

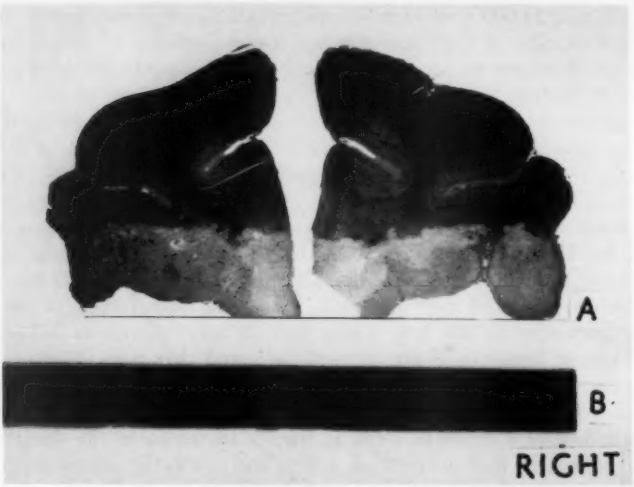


FIG. 1. *A.* Coronal section of frontal lobes of monkey demonstrating frontal lobotomy by radiation destruction. Note homogenity of radiation damage and absence of side-scatter. Weil preparation. *B.* Actual appearance of experimental beam of 23 mev. x-rays used. Beam was fired from right to left.

result of the vascular changes noted. It is unnecessary to review the entire literature on this subject for this report but such a review is being undertaken.

EXPERIMENTAL PROCEDURE

Healthy adult monkeys (Macaca mulatta) of both sexes, weighing 2.5 to 4 kg., were exposed under Nembutal anesthesia to single total-doses of 23 mev. x-rays from the betatron via a 1 cm. or 2.5 cm. circular portal. The actual appearance of the beam can be seen in figure 1B. The radiation was directed transtemporally or transfrontally. To date a rather wide range of single doses of 23 mev. x-rays, from 375 r to 14,000 r, has been studied. This dose range of 375 r to 14,000 r of 23 mev. x-rays is equivalent in biologic effectiveness to 225 r to 8,400 r of 400 kev. x-rays.[12–15] This decreased effectiveness of high energy radiations has been observed in both our clinical and experimental studies. It is due primarily to the difference in specific ionization,[16] that is to say, a smaller number of ionizations occur with the high speed radiation of the betatron in the same unit of length (micron) of pathway in the tissues, than occurs in the same unit of pathway with the conventional low energy x-ray beam (200-400 kev.). The high energy radiations employed in this study yield approximately 8.5 ion pairs per micron of pathway through tissue, whereas low energy x-rays (200–400 kev.) yield 80 ion pairs. Therefore, although low energy x-rays produce ten times the number of ion pairs per micron of tissue as do high energy radiations, the effectiveness of low energy x-rays is only approximately 40 per cent greater. Thus, the range of

doses, 375 r to 14,000 r, of high energy radiations employed in this study is equivalent to 225 r to 8,400 r of 400 kev. x-rays, utilizing a conversion factor of 0.60 which is now an acceptable factor for the approximate biologic effectiveness of 23 mev. x-rays.

In the actual radiation exposure the monkey's head was held horizontally by means of a specially devised holder so that the entry-portal of the beam was in the right temporal or frontal region and the exit-portal was in the left temporal or frontal regions, respectively. The dose-rate of irradiation with the 1 cm. beam was 150 r/min.; the dose-rate with the 2.5 cm. beam was 75 r/min. No filter was necessary with the 1 cm. beam, whereas a compensating filter was employed with the 2.5 cm. beam. In all cases the target-skin-distance was 83.4 cm. Figure 2 shows the appearance of the dose-distribution curve of 400 kev. x-rays and 23 mev. x-rays, as measured in centimeters of depth in water. It will be noted that with 400 kev. x-rays the maximum dose (maximum ionization) occurs immediately, and thereafter the dose decreases exponentially. On the other hand, 23 mev. x-rays have their maximum dose at a depth of 4 cm. in water. Inasmuch as the tissues of the body have a very high content of water, and since the atomic number of tissues is only slightly higher than water, the maximum dose of 23 mev. x-rays in tissues will be at an approximate depth of 4 cm. A 3.4 cm. block of lucite was placed against the right side of the monkey's head in order to increase the intensity of ionization to about the 100 per cent peak of the dose-distribution curve of 23 mev. x-rays. Since the dose-distribution curves of the 1 cm. and 2.5 cm. beams of 23 mev. x-rays have, at their peak-intensities, a nearly flat plateau of 90–100 per cent ionization for the next 4.5 cm. of tissue penetration, and since the average transfrontal and transtemporal diameters were 5 cm. in the monkeys selected for radiation, it was possible to maintain an almost uniform tissue-dose-distribution through the monkey's brain. The sketch of the monkey's head (B) in figure 2 shows the position of the head with respect to the dose distribution curve. In this figure, A represents the block of lucite, 3.4 cm. in thickness, which was employed to absorb the ascending portion of the dose-distribution curve of 23 mev. x-rays. The monkey's head was placed in direct contact with the lucite block at the point of maximum ionization, that is, the 100 per cent peak at 4 cm. depth. By actual determination the entry-skin-dose was 100 per cent of the total-dose, and the exit-skin-dose was 90 to 95 per cent of the total-dose. This almost complete uniformity of dose-distribution through the monkey's brain, obtainable with 23 mev. x-rays from the betatron, made it possible to detect bilateral areas of comparable radio-responsiveness within the brain. In addition to the betatron's experimental advantage to deliver a more uniform tissue-dose, the 1 cm. and 2.5 cm. beams of x-rays used remained so well collimated that the area of epilation on the exit-side was no more than a millimeter larger in diameter than the epilated area at the entry-side.

Following the administration of the selected total-dose of radiation at a single exposure, each animal was carefully observed for any clinical evidence

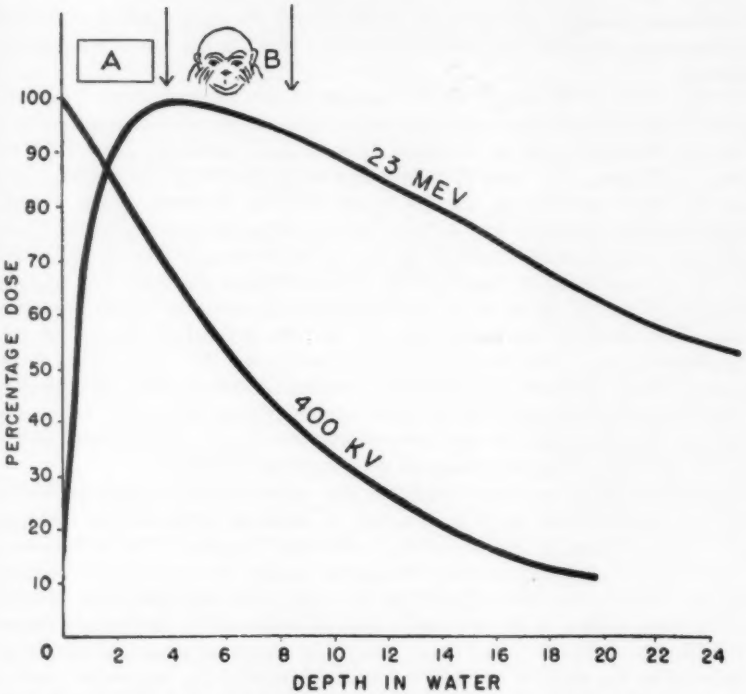


FIG. 2. Comparison of the dose-distribution curves of 400 kev. x-rays and 23 mev. x-rays, as measured in centimeters of depth in water. *A* represents the block of lucite utilized to absorb the first 4 cm. of the ascending portion of the dose-distribution curve of 23 mev. x-rays. *B* represents the position of the monkey's head in dose-distribution curve of 23 mev. x-rays.

of radiation damage. In this present report, the longest period of observation after irradiation was 24 months; however, additional monkeys have now been observed beyond the two-year period, particularly those monkeys receiving the lowest doses, but their brains have not been completely studied as yet. The animals were sacrificed with intravenous Nembutal, and the intact brains were perfused with 10 per cent formalin via the carotid arteries after preliminary washing with isotonic saline solution. The brains were then fixed in large volumes of 10 per cent formalin for ten days to two weeks, imbedded in celloidin, and the entire brain serially sectioned at 20 microns. Three series were made beginning with sections 20, 21, and 22 and every twentieth section saved thereafter, and Nissl, Weil-van Gieson, and hematoxylin-eosin preparations made. In addition a few brains have been removed without perfusion, fixed in various fixatives, and special silver impregnations carried out. A number of the monkeys died during the first few days after radiation, particularly those monkeys exposed to the larger lethal doses with the 2.5 cm. beam.

Additional monkeys were allowed to go through the entire period of delayed radionecrosis in order to determine the lethal effect of the lowest dose administered.

The choice of utilizing a small 1 cm. or 2.5 cm. beam of x-rays was made, rather than carrying out total irradiation of the head, so that sufficient nonirradiated brain would be available to serve as a histologic control for the irradiated areas. The average dimensions of the brain of the monkeys used in this series were 6 cm. for the fronto-occipital diameter, 4 cm. for the transtemporal diameter, and 3.2 cm. for the vertex-to-base diameter. Therefore, for those monkeys exposed to the 1 cm. beam of radiation, there was 5 cm. of nonirradiated tissue in the fronto-occipital diameter and approximately 2.2 cm. of tissue in the vertex-to-base diameter for control examination. The monkeys irradiated with the 2.5 cm. beam had 3.5 cm. of nonirradiated tissue in the fronto-occipital diameter and 0.7 cm. of tissue in the vertex-to-base diameter for histologic control. Consequently, each monkey was essentially a control for its own irradiated area of brain, and by this method it was possible to rule out postmortem changes and artifacts, and to detect the early changes leading to delayed radionecrosis.

More recently, we have irradiated the entire brain of monkeys with a 7.5 cm. circular beam of 23 mev. x-rays, in order to determine the comparative responsiveness of all the different areas and regions of the central nervous system. In such total-head irradiation studies, however, single doses of 23 mev. x-rays over 5,000 r could not be given since this represents an acute lethal dose; 3,000 r of 200–400 kev. x-rays administered to the monkey's brain was likewise an acute lethal dose. When the entire brain and brainstem are included in the field of irradiation long term studies are impossible, since a dose of 3,000 r of 23 mev. x-rays (1,800 r of 400 kev. x-rays) will kill in six to eight months as a result of extensive delayed radionecrosis occurring in the brainstem. Hence, the use of the small 1 cm. and 2.5 cm. beams of 23 mev. x-rays allows one to employ a much wider range of radiation doses and to observe the responses over longer periods of time. The reactions observed with the small beam can be better controlled.

Electroencephalographic recordings have also been made in many of our irradiated animals. Another small group of monkeys has received a range of single doses of 23 mev. x-rays through one hemisphere by administering the radiation in the transfronto-occipital field. Thus, with only one hemisphere irradiated, usually the right, the opposite nonirradiated hemisphere could serve as a control for electroencephalographic studies. By this experimental method we have been able to detect electroencephalographic changes with as little as 375 r of 23 mev. x-rays (225 r of 400 kev. x-rays). These studies will be detailed in a future report.

The neurologic comments in this report are based upon observations in 65 irradiated animals, whereas the histologic findings are from an analysis of many thousands of sections of 40 brains which were prepared as outlined above.

TABLE 1

SPECTRUM OF HISTOLOGIC CHANGES POSTRADIATION

Tissue Doses: 1. Betatron (r) (23 mev.) 2. Dose in x-ray r (400 kev.)*	Acute stage (1 day–6 wks.)	Intermediate stage (6 wks.–5 mos.)	Late stages (5 mos.–8 mos.)	Late stages (8 mos.–12 mos.)	Late stages (12 mos.–24 mos.)
1. 7,000–14,000 r 2. 4,200–8,400 r	Acute necrosis of all neural components and small vessels. Large vessels patent.	Acute stage persists. No recovery. No gliosis.	Little or no gliosis in adjacent tissues.		
1. 5,000–7,000 r 2. 3,000–4,200 r	Acute inflammation, hemorrhages, perivascular exudates, partial necrosis, myelin changes, edema. Abnormal EEG.	Partial recovery histologically. Abnormal EEG.	Delayed, nonselective diffuse radionecrosis. Abnormal EEG.	Very slight gliosis of radioactive areas. Vascular hyalinization. Abnormal EEG.	Moderate to intense gliosis of radionecrotic areas. Obliterated vascular channels. Abnormal EEG.
1. 3,000–5,000 r 2. 1,800–3,000 r	Acute inflammation, hemorrhages, perivascular exudates, edema. Abnormal EEG.	Complete recovery histologically. Abnormal EEG.	Delayed radionecrosis (selective for white matter). Deficient gliosis. Abnormal EEG.	Mild gliosis of radionecrotic white matter. Vascular changes. Abnormal EEG.	Intense gliosis. Abnormal EEG.
1. 1,500–3,000 r 2. 900–1,800 r	Acute inflammation, exudates, edema. Abnormal EEG.	Complete recovery histologically. Abnormal EEG.	Mild degenerative changes in myelin. Abnormal EEG.	Delayed radionecrosis (selective for white matter). Deficient gliosis. Abnormal EEG.	Mild gliosis. Abnormal EEG.
1. 375–1,500 r 2. 225–900 r	Studies incomplete. Abnormal EEG.	Studies incomplete. Abnormal EEG.	Studies incomplete. Abnormal EEG.		

*Equivalent dose of 400 kev. x-rays based on biologic effectiveness.

EXPERIMENTAL RESULTS

Table 1 is a summary of the pathologic findings and general electroencephalographic observations in our animals as related to the specific tissue-dose of 23 mev. x-rays administered. Beneath each dose of 23 mev. x-rays, the equated-dose of 400 kev. x-rays is given. In each case, a conversion-factor of 0.60 was used in determining these equated-dosages since the roentgen unit (r), as delivered by the betatron at energies of 23 mev., is about 40 per cent less effective, biologically, than the r as produced by the conventional x-ray machine at 200–400 kev. The explanation for this difference in effectiveness has already been given under experimental procedure.

Effects of 7,000–14,000 r of 23 mev. x-rays (equivalent to 4,200–8,400 r of 400 kev. x-rays)

Single tissue-doses of 7,000 r or more of 23 mev. x-rays produce an acute necrosis of the entire area traversed by the beam of x-rays. In this dose-range there is no evidence of radio-selectivity, since all the neural components irradiated were destroyed throughout the pathway of the beam. The larger blood vessels still remained intact. Figure 1A shows a coronal section through the frontal lobes of a monkey, which had received 7,000 r (23 mev. x-rays) in

a single dose through the base of its frontal lobes with the intent of producing a frontal lobotomy. This was obviously accomplished, and the monkey remained lobotomized, clinically, up to the time of sacrifice at six weeks. Such large tissue-doses of 7,000 r or more, given in a single exposure, were not incompatible with survival of the animal, provided the radiation traversed only the cerebral cortex and not the brainstem or hypothalamus. From our studies, the brainstem and hypothalamus appear to be particularly vulnerable to the effects of radiation.

The betatron x-ray beam can produce a fairly sharply demarcated zone of destruction. At first there is very little or no reaction to be observed in the nonirradiated neural tissue adjacent to the destroyed area, except for a slight increase in the number of astrocytes. The early inability of the glial cells to react following radiation has been a constant finding in our studies. Eventually the glial responses recover at approximately one year postradiation and marked glial scarring occurs in the irradiated area.

Effects of 5,000–7,000 r of 23 mev. x-rays
(equivalent to 3,000–4,200 r of 400 kev. x-rays)

In the dose-range of 5,000–7,000 r of 23 mev. x-rays, the acute pathologic findings observed were inflammatory reactions, edema, hemorrhages, perivascular exudates, disturbances in the white matter, and occasional small areas of acute necrosis. The acute inflammatory responses, edema, and hemorrhages slowly resolved in the ensuing weeks, but the areas of necrosis persisted. The damage to white matter appeared to recover in part. All the monkeys in this dose-range showed extensive clinical manifestations of their irradiations, such as quadriplegias, generalized seizures, and reductions of state of consciousness. These clinical findings become apparent upon recovery from anesthesia or appeared very rapidly within the first 24 hours after the radiation had been given, and reached their maximum intensities at three to four days. Thereafter, the seizures subsided and a more normal state of alertness returned. Each animal's quadriplegia improved much more slowly, so that by the end of two weeks or more a moderate quadriparesis with hyperreflexia was still evident. By four to five weeks postradiation, all evidence of muscular weakness was gone, and all the monkeys were well clinically, with the exception of an occasional monkey which would show a persistent hyperreflexia beyond the acute period. This persistent hyperreflexia could be related to the small areas of acute necrosis and damage to the white matter occurring in the upper limits of the dose-range of 5,000 to 7,000 r. The majority of the monkeys, however, upon recovery from their acute neurologic syndromes, remained well, clinically, for a period of four months or longer. Then there appeared, rather abruptly at this late stage, a number of intense and rapidly progressive neurologic disorders due to delayed radionecrosis. Monkeys that had been physically well and neurologically negative during the intermediate period, except for abnormal electroencephalographic patterns, now became rapidly apathetic and quadriparetic. Within a relatively short period of a few weeks, these

monkeys rapidly worsened, became quadriplegic and comatose, and finally expired. Microscopic examination showed extensive nonselective radionecrosis throughout the entire path of the beam and only in the path of the beam.

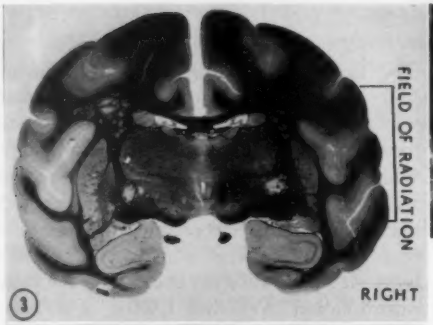
Effects of 3,000–5,000 r of 23 mev. x-rays
(equivalent to 1,800–3,000 r of 400 kev. x-rays)

In the dose-range of 3,000–5,000 r of 23 mev. x-rays, the clinical effects, which were also apparent following recovery from anesthesia, were less severe than those observed in the monkeys receiving the higher doses of high energy radiations. There appeared in these animals a definite reduction of the level of consciousness, occasional generalized seizures, and a mild quadriparesis, with an associated hyperreflexia. These acute clinical signs usually subsided within the first week, so that each monkey shortly regained its preradiation level of alertness and muscle strength. Hyperreflexia tended to persist for an additional week in an occasional monkey, but thereafter all monkeys in this dose-range remained neurologically negative until the onset of delayed radionecrosis some six to eight months later. Histologic examination of the brains of the monkeys sacrificed during the acute stage of 3,000–5,000 r dose-range revealed very intense inflammatory reactions, hemorrhages, exudates, and edema throughout the irradiated part of the monkey's brain. It should be pointed out at this time that some of the acute inflammatory cells spread beyond the specifically irradiated area and produced a moderately diffuse meningoencephalitis. This diffuse meningoencephalitis appeared to be responsible for the generalized seizures and depression of the level of consciousness observed in all the monkeys during the acute stage. This diffusely spreading inflammatory process was more extensive with the larger 2.5 cm. beam of x-rays and it was more intense with the higher doses administered. In passing, it should be pointed out that patients receiving courses of x-ray therapy for neoplasms of the brain not infrequently show an aggravation of their symptoms plus headaches, nausea, and vomiting (radiation sickness) during their course of therapy. This phenomenon of radiation sickness can now perhaps be best explained by two factors: 1) the acute inflammatory reactions and edema of the specific area irradiated, and 2) the diffusion of the inflammatory reactions beyond the irradiated area, so as to give rise to an acute meningoencephalitis. This spreading inflammatory process is usually maximum in the areas adjacent to the area irradiated.

Those monkeys that received 3,000 r to 5,000 r of high energy radiations were neurologically well in all respects during the intermediate period, except for an abnormal electroencephalogram. Animals sacrificed during this period showed only very mild nervous and glial cell changes. These cellular alterations were present only in the pathway of the beam, and would have been difficult to detect had there not been considerable nonirradiated, control areas in the same and adjacent brain sections for comparison. Essentially, therefore, these monkeys showed a virtually complete recovery during the intermediate stage and then some six to eight months later, they developed a less fulminat-

ing course of delayed radionecrosis which was strikingly selective for the white matter. This delayed radio-selectivity for the white matter occurred only in the irradiated area and never extended beyond the size of the beam of radiation employed. The changes in the cortical neurons were moderate in comparison to the severe changes appearing in the white matter. However, the neurons of the paraventricular and supraoptic nuclei of the hypothalamus were seriously damaged. The white matter of the deeper portions of the centrum semiovale, the corpus callosum, internal capsule, and brainstem was more responsive than the more superficial cortical white matter. Figure 3 shows almost symmetrical areas of damage to the white matter occurring in the internal capsule and the centrum semiovale of both sides, as compared with a normal brain (figure 4). Such symmetry of radiation-response is possible with high energy radiations, when the irradiation exposure is carried out in the manner employed in this study. The white matter of the brainstem was most responsive, and all monkeys exposed to a dose of 3,000 r of 23 mev. x-rays, in which the radiations traversed the brainstem, died at approximately eight months postradiation, because of the serious damage to the brainstem. Figure 5 shows the marked damage to white matter in the brainstem at six months after 3,000 r of 23 mev. x-rays. This dose of 3,000 r of high energy radiations is equivalent to 1,800 r of 400 kev. x-rays.

The disintegration of the white matter appears to be degenerative in nature, beginning in part as a demyelinating process and then progressing to an actual necrosis of all the white matter constituents, that is, the myelin, axons, and glial cells. The reactive processes within and around the broken-down areas are surprisingly deficient or very minimal at this time-interval of five to eight months postradiation in this dose range. There are no histologically recognizable vascular changes which might account for the extensive damage observed. However, a very interesting sequence of pathologic changes occurred in those monkeys which had not been irradiated through the brainstem and could, therefore, continue to survive indefinitely. At approximately ten to 12 months postradiation, the areas of radionecrosis within the white matter of these monkeys were slowly becoming filled in with glial cells. By 24 months these areas were heavily gliosed and numerous binucleated as well as multinucleated glial cells were present, but no excessive mitotic activity or abnormal growth patterns suggestive of neoplasia were apparent at this time. At 12 months postradiation a moderate thickening of the vessel walls became evident in those vessels residing in the degenerated areas within the white matter, whereas there were no vascular alterations in vessels in the cortex or in the more resistant areas of white matter which lay in the same irradiation pathway as the degenerated areas. Hence it would appear from this study that the vascular changes and obliteration of vascular channels were for the most part secondary to the death or degeneration of neural tissues, rather than a primary effect of radiation.



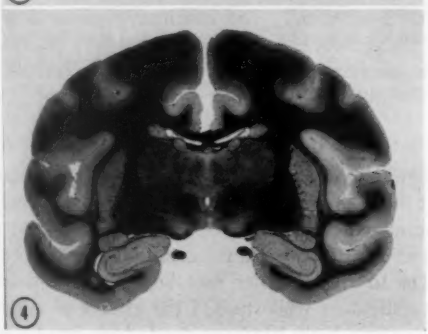


FIG. 3. Delayed radio-selectivity for the white matter appearing in the centrum semiovale and internal capsule bilaterally. Note the symmetry of response.

FIG. 4. Compare this photograph at the same level of section from a normal brain with figure 3.

FIG. 5. Extensive delayed radionecrosis in the white matter of the brain stem at six months following 3,000 r of 23 mev. x-rays (equivalent to 1,800 of 400 kev. x-rays).

Effects of 1,500–3,000 r of 23 mev. x-rays (equivalent to 900–1,800 r of 400 kev. x-rays)

Following exposure to 1,500–3,000 r of 23 mev. x-rays, the acute clinical and histologic findings were less severe and shorter in duration. With an exposure of 1,500 r of 23 mev. x-rays (900 r of 400 kev. x-rays) moderate inflammatory reactions, cellular alterations, and cerebral edema could be readily detected, but overt clinical neurologic findings were difficult to detect. However, electrical activity of exposed areas was depressed following irradiation.

Within two to three weeks the acute histologic reactions resolved and the depressed electrical activity recovered in part. At approximately three months postradiation, the electroencephalogram began to show spiking activity in the irradiated areas, but at this time no clear-cut neurologic findings were observed. However, at a year or more postradiation a persistent hyperreflexia and an increased tone of the extremities appeared. Some of the animals began to have clinical seizures which were at first focal, then generalized in nature. Histologic studies at this time revealed radiation damage primarily in the brainstem and internal capsules, and some moderate changes in the hypothalamus. Although there were definite changes in the cells of the cerebral cortex, the cells were not destroyed but rather were altered in morphology.

Effects of 375–1,500 r of 23 mev. x-rays (equivalent to 225–900 r of 400 kev. x-rays)

In this lowest dose range studied to date, the histologic studies are incomplete as yet. Although immediately postradiation no clinical findings could be observed, the electroencephalogram showed definite depression of electrical activity. Months later the electroencephalogram began to show spiking activity. The details of these latter findings will be reported later. Those monkeys which received 375 r of 23 mev. x-rays have not been followed long enough to determine whether they will show delayed radiation changes at some prolonged interval postradiation. However, those monkeys which received 750 r or 1,500 r of 23 mev. x-rays have shown delayed radiation changes in the more responsive areas a year or more postradiation. Whether 1,500 r of 23 mev. x-rays (equivalent to 900 r of 400 kev. x-rays) will eventually cause death has not been determined as yet. As previously indicated, 3,000 r of 23 mev. x-rays causes death within six to eight months provided the radiation traverses the brainstem.

DISCUSSION

Evaluation of the histopathologic effects of radiation on any normal tissue is difficult in view of the fact that the responses to x-irradiation are frequently slow and insidious in their development. The appearance of neoplastic changes in a normal tissue many years after irradiation is an outstanding example of this insidious capacity of radiations to alter cellular metabolism and cellular morphology.[17] Many previous investigators who studied the effects of x-rays upon the intact central nervous system have not examined their irradiated tissue at frequent intervals over a prolonged period of time after radiation, and thereby failed to observe the entire sequence of pathologic events that can occur. Then, too, in previous studies the entire brain was irradiated and, as a consequence, the investigator had no available nonirradiated cerebral tissue in the same or adjacent sections to serve as a control for comparison in detecting the more subtle changes which can occur in the constituents of the central nervous system following exposure to low dosages of radiations. Our study was greatly facilitated by the experimental advantages inherent in the well-defined, penetrating, and homogeneous beams of x-rays obtainable with the betatron. Furthermore, our method of histologic study, that is, by serial sections of the entire brain, which had not been employed in previous studies, enabled us to detect the radio-responsiveness of the various structural components of the brain, as well as the areas of greatest responsiveness.

We believe, from our observations, that the central nervous system is much more radio-responsive than generally conceded. It can show electroencephalographic abnormalities following an exposure to a dose as low as 375 r of 23 mev. x-rays (equivalent to 225 r of 400 kev. x-rays), which would indicate a reaction of the neurons to irradiation. Whether the central nervous system will respond to lower doses of radiation remains to be determined, since 375 r of 23 mev. x-rays is the lowest dose administered to date.

The demonstration that 7,000 r or more of 23 mev. x-rays will produce an acute necrosis of the frontal lobes suggests the possibility of utilizing radiation as a means of performing frontal lobotomies. Monkeys will certainly tolerate such large single doses of x-rays, provided the size of the beam is kept small and vital areas such as the brainstem and hypothalamus are avoided. This may be true for the brain of man as well, but the specific dose of high energy x-rays required for such an effect in man remains to be determined. High energy electron beams, which the betatron can also produce, would appear to be more feasible in such proposed radiation lobotomies, since high energy electrons can be delivered at a rate of 1,000 r per minute, whereas the ordinary output of high energy x-rays is only approximately 100 r per minute. The use of high energy electron beams would, therefore, shorten considerably the exposure time required for such radiation lobotomies. Studies in radiation frontal lobotomy as well as temporal lobotomy in monkeys with the use of the electron beam will be reported.

The appearance of delayed radiation damage in the brain of monkeys following exposure to single doses of x-rays as low as 1,500 r of 23 mev. x-rays (equivalent to 900 r of 400 kev. x-rays) does not in any way imply that such a phenomenon will occur with a tumor dose of 1,500 r, given in a fractionated course to a patient with a brain tumor. A dose of x-rays, when highly fractionated over a period of weeks, will usually give less in the way of a histologic response than the same dose given in a single exposure. It would, therefore, be incorrect to extrapolate to man the present dose-data obtained in the monkey, but on the other hand the type of histologic responses detected in our experimental animals have been noted in our patients receiving x-ray therapy and can, therefore, be applied to man. In addition, we have now observed a number of patients in whom delayed radionecrosis has occurred a year or more after radiation, following a tumor dose of 4,000 r of 200–400 kev. x-rays given in one or more well fractionated courses, and following a tumor dose of 6,000–7,500 r of 23 mev. x-rays given in one fractionated course.

This capacity of radiations to cause a delayed radionecrosis, which may be fatal if it occurs in the brainstem, should be given considerable thought when planning a course of radiation therapy for those patients with more centrally located neoplasms, particularly if the lesion is rather slow in its rate of growth. It would appear wiser to give such benign centrally-positioned lesions, which are not excisable, much less radiation than generally given, with the intent of producing an inhibition of the rate of growth of the tumor rather than attempting a destruction of the lesion. On the other hand, when dealing with the more malignant deeply-situated neoplasms where survival without therapy may be a matter of weeks or months, the therapist can employ large doses of radiation in an effort to inhibit or destroy the growth. However, when such large doses of x-rays are given in an effort to prolong the life of the patient beyond his natural survival expectancy without irradiation, they should be given with the preknowledge of potential delayed radionecrosis a year or more postradiation. In treating the malignant cortical neoplasms, such as the

glioblastoma multiforme, which can rarely be completely excised, it may be therapeutically advisable to give a large specific tumor dose to destroy such a lesion and then, when delayed radionecrosis appears in the irradiated areas, to excise the necrotic tissues which have a tendency to behave as a swollen tumor mass in some cases. This method of approach to the treatment of the glioblastoma multiforme would, of course, yield patients "cured" of their lesion, but serious neurologic deficits would remain in some patients.

SUMMARY

1. The central nervous system is more radio-responsive than generally supposed.

2. The effects of high energy x-rays on the brain of monkey and man appear to be direct effects and are not secondary to vascular occlusion.

3. The brainstem appears to be most responsive to radiation.

4. The white matter of the deep portions of the centrum semiovale, internal capsules, and brainstem are peculiarly responsive to x-irradiation.

5. The cells of paraventricular and supraoptic nuclei of the hypothalamus are responsive to x-rays.

6. Comparable radiation responses are being observed in patients receiving x-ray therapy for tumors of the central nervous system.

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Clinical Observations on Aphasia

Hildred Schuell, Ph.D.

AT THE PRESENT TIME the literature on the subject of aphasia is increasing, but in general it follows two extremes. On the one hand there is a tendency to oversimplify the entire field, while on the other the material is so confused that the average clinician dismisses the whole subject and thus fails to use important information which could contribute to the clinical handling of patients.

It is the purpose of this paper to report test findings on 65 aphasic patients, and to describe certain basic patterns of aphasic impairment which may be helpful to the clinician.

When the language behavior of aphasic patients is observed in a comprehensive, uniform, and systematic manner, two kinds of information are gained. First, such observations yield information about the individual components of aphasia. Essentially this is a description of the ways in which the language behavior of aphasic patients differs from that of nonaphasic individuals. Secondly, certain patterns of aphasic impairment become evident. These are the observable relations between groups of symptoms which tend to recur. Three basic patterns which can be identified by relatively simple means and their prognoses will be discussed.

CASE MATERIAL

Subjects were 65 aphasic male patients examined consecutively at the Minneapolis Veterans Administration Hospital, ranging in age from 19 to 65 years. Forty-two per cent of the group were over 50. Cerebrovascular accidents were responsible for 55 per cent of the disabilities.

On admission to the hospital all patients were examined with a battery of diagnostic tests developed in its Aphasia Center, including tests for understanding spoken language, for spoken language, reading, writing, arithmetic processes, and selected performance tests. Details of tests will not be described since it is the purpose of this paper to emphasize observations of aphasic performances rather than testing methods.

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OBSERVATIONS

Four important conclusions can be drawn from analysis of test records. In some cases these conclusions conflict with those previously reported in the literature, but there were no important exceptions to the following:

1. No isolated pure disorders of speech were found.

2. Partial rather than total disabilities were most commonly observed for all language functions.

3. Although patients showed inconsistencies on individual responses, percentages of errors tended to remain stable on retesting, or showed gradual decreases as patients responded to therapy.

4. Sharp lines could not be drawn between functions tested, since impairment of one function was often reflected in another, particularly at higher levels.

Most patients showed impairment in all functions tested. This does not mean that specific disabilities did not appear. They did, but in combination with other, often less obvious disabilities. Analysis of even mild aphasic impairment usually makes it possible to trace difficulties back to basic auditory, visual, or motor involvement. This would tend to indicate that close study of aphasic conditions should yield more and not less localizing data in the future.

The second and third observations are important in that together they indicate that stable patterns can be observed and basic disabilities analyzed in spite of apparent inconsistencies of performance. Thus underlying problems can be identified and treated more effectively.

The fourth observation indicates that qualitative as well as quantitative analysis of aphasic findings is necessary in order to determine what factors are operating and avoid superficial and misleading diagnoses. It is necessary to know not only what items the patient cannot perform, but why he cannot perform them. When comprehensive testing is done, this is indicated by the patterns of impairment which emerge.

Table 1 shows the number and percentage of patients who made errors on tests administered. It is readily apparent that all patients showed defects in more than one language function. Although careful testing usually reveals involvement of all language functions, specific disabilities predominate and form the basis for each clinical picture which emerges. The underlying disability and the role it plays in the total aphasic pattern can be determined by relatively simple testing. Since aphasic defects can be readily observed, provided the examiner has a clear understanding of what to look for and of the part a specific disability may play in over-all language performance, each of the major functions involved, together with methods of observation and obtained findings, will be discussed separately. These include: 1) auditory impairment; 2) speech and language impairment; 3) visual (reading) impairment; 4) visuo-motor (writing) impairment; and 5) conceptual impairment including arithmetic processes.

TABLE 1

RESULTS OF LANGUAGE FUNCTION TESTS AMONG 65 APHASIC SUBJECTS

Language functions tested	*Patients making errors*	
	Number	*Per cent*
1. *Auditory impairment*		
Recognizing single words	15	23
Understanding spoken language	65	100
2. *Speech and language impairment*		
Phonation	19	29
Tongue movements	19	29
Repetition of words	27	42
Repetition of phrases	44	68
Naming (word-finding)	39	60
Functional speech	52	80
Abstract language	65	100
3. *Visual (reading) impairment*		
Recognizing objects	2	3
Recognizing single words	15	23
Reading comprehension	65	100
4. *Visuo-motor (writing) impairment*		
Copying	20	31
Revisualizing objects	31	48
Spelling	52	80
Writing to dictation	60	92
Spontaneous writing	59	91
5. *Conceptual impairment*		
Arithmetic	65	100
Performance tests	65	100

AUDITORY IMPAIRMENT

Auditory impairment appears to be one of the most important of all language disabilities. Impairment can be readily detected by simple tests which have a high predictive value for recovery from aphasia. These include pointing to common objects named by the examiner, following directions of increasing length and complexity, and indicating comprehension of longer units of speech by answering yes or no to questions about materials presented.

Twenty-three per cent of the patients examined made errors on the simplest test, recognition of names of common objects. These patients tended not to recover functional speech.[1] The rest of the group, who were less severely involved, were able to recognize objects named and sometimes showed superior ability in vocabulary recognition. Nevertheless they had marked difficulty in following directions and in responding appropriately to longer units of spoken language. Degree of involvement was variable. Some patients were able to follow short directions, but not two of these combined; some two, but not three. Errors increased as length of materials was increased.

These patients generally responded well to therapy, and were able to handle longer and longer units adequately as therapy progressed, indicating that the disability is reversible to a considerable degree. This disability is one that may be readily overlooked, since it may not be apparent unless the patient is tested with units of progressive length and required to make a specific response to each item.

In the area of auditory impairment, therefore, two basic disabilities exist: first, impairment of recognition of common words, which may be considered an auditory agnosia and carries a poor prognosis; and second, impairment of ability to grasp longer units of language, although word recognition is retained, a condition which is largely reversible. The latter appears to be a retention impairment. It is thought to stem from impairment of ability to reauditorize language sequences, and thus may be termed an impairment of reauditorization.[1,2] Because of its importance in relation to all language functions and because it is frequently overlooked in routine examinations of aphasic patients, the following simple test methods are suggested to detect this impairment.

If the patient can talk:

1. Repetition of words, gradually increasing length of syllables.
2. Repetition of digits, gradually increasing number of digits.
3. Repetition of sentences, gradually increasing in length.

If the patient cannot talk:

1. Following directions of progressive length.
2. Following two, then three, short directions combined.
3. Pointing to combinations of two, then three objects in a picture (such as, "*Show me the house, the road, and the windmill*").

As will be seen later, the importance of auditory impairment in relation to aphasic disorders probably cannot be overemphasized, since it interdigitates with many other speech functions, influencing patterns observed and resulting prognosis.

LANGUAGE IMPAIRMENT

The language impairment of an aphasic patient can be most readily understood if the clinician asks himself four questions: 1) to what extent is the motor mechanism involved; 2) how much difficulty does the patient experience finding the words he wants; 3) to what extent is he able to communicate his simple everyday needs and feelings (functional speech); and 4) to what extent can he use language to express more complicated relations (abstract language). Each of these aspects of language will be discussed briefly in relation to aphasic findings.

Motor functions. Although it is necessary for the patient to obtain voluntary control of the muscles used in speech, detailed discussion of this kind of involvement will be omitted since these factors are well-known to most physicians. However, it is necessary to be aware that defects of reauditorization may simulate motor disabilities very closely. They may be differentiated as follows:

MOTOR IMPAIRMENT

1. Errors tend to be consistent. Some speech sounds are impaired more than others, and these are impaired whenever they occur.
2. Sounds requiring more difficult positions and coordinations and consonant combinations are impaired more than sounds with uncomplicated movement patterns.
3. Patients have difficulty repeating even short familiar words that contain difficult sounds. They have less difficulty if allowed to utilize visual and placement cues.
4. All voluntary speech shows the same degree of hesitancy and laboriousness.

AUDITORY IMPAIRMENT

1. Errors are inconsistent. Sounds are used correctly at some times and not at others.
2. Patients sometimes pronounce difficult words effortlessly and make errors on easy ones.
3. Patients are soon able to repeat short units readily, and only have difficulty when length is increased beyond retention span.
4. Patients soon acquire some speech that is normal and fluent, although vocabulary may be limited and word-finding errors occur.

The fact that more patients had difficulty repeating phrases than repeating words emphasizes the relationship between reauditorization and speech. Test records indicate that errors increased in direct ratio to length of phrase employed. In connected speech rehearsals of words and struggle behavior similar to that observed in stuttering again simulate motor disabilities, but these usually occur when the patient cannot "hear" the word he wants to say. Auditory stimulation often results in dramatic improvement of speech, both in accuracy and fluency.

Word-finding. The inability of the aphasic patient to say the word he wishes to say is one of the most frequently observed aphasic symptoms. This has been widely discussed in the literature under headings of anomia, amnesic aphasia, and paraphasia. Sixty per cent of the patients in the present series made errors naming common objects. The kinds of errors observed were:

1. Jargon (completely unintelligible responses).
2. Distortions (approximations of desired responses).
3. Paraphasia (use of an inappropriate word).

Paraphasia has been variously defined, but it is considered more meaningful to reserve this term for that large category of responses in which the patient uses a word that is strongly associated with the desired word (such as *chair* for *bed*, or *hot* for *cold*) but is not synonymous with it.[3]

It is probable that word finding disabilities result from impairment of ability to evoke specific auditory patterns. Through associations either of sound or meaning, the patient gets close to the word he wants but often cannot evoke it unaided. In the author's experience subjecting the patient to a barrage of controlled auditory stimulation is the most effective treatment for word-finding difficulties.

Functional speech. For present purposes, functional speech is defined as ability to make appropriate responses at a relatively simple level of communication. Patients were asked to give certain information about themselves, to tell what was happening in a picture, and what they had done during the day. All language requested was about things immediately at hand or in the direct experience of the patient. Eighty per cent of the patients tested showed

some impairment at this level. Most failures stemmed from impairment of word finding. Mild degrees of impairment, which did not appear when patients were asked to name familiar objects, became apparent when the patient attempted to make specific responses and to communicate his own ideas at greater length.

Abstract language. This is the highest level of language function, and impairment may be overlooked unless special testing methods are used. It is important that it be evaluated, for patients with adequate speech for conversational purposes may still have too much aphasic impairment to be able to return to occupations requiring even moderate language proficiency. Usually the disability may be observed if the patient is asked to formulate sentences using given words and to explain metaphoric expressions, similarities, and proverbs. All patients tested made some errors at this level. They were inclined to give literal and concrete responses associated with one aspect of the stimulus, but were unable to deal with more than one concept at a time or to integrate the statements they had made, usually because they could not remember them. Often they produced chains of associations getting farther and farther away from the original intent until it was lost entirely. The quality of these responses changed as patients acquired more available language. Direct relationships appeared between ability to reauditorize, extent of vocabulary, and ability to formulate ideas, first simply, then on more abstract levels.

There is, of course, an overlap with intelligence. It is necessary to evaluate these responses in relation to educational and vocational level, extent of aphasic impairment, and changes which occur as language increases.

VISUAL IMPAIRMENT

Patients were tested for ability to 1) recognize objects, 2) recognize symbols, and 3) read units of progressive difficulty. Only two patients in the series had difficulty recognizing objects and both showed gradual recovery. Other patients reported having previously experienced this disability, but at the time of testing only difficulty recognizing symbols was observed. It should be noted that impairment of visual recognition of symbols may easily be confused with impairment of auditory recognition. In general, patients with auditory impairment tend to confuse symbols whose names sound alike, such as C D E G V, A H J K, and F S X, while patients with visual impairment have more difficulty with symbols having similar visual components, such as p b d q, h n u, A N V, and B P R. In reading words they tend to reverse letters and read *saw* for *was* and *ton* for *not*, and to confuse words which look alike such as *beat* and *boat* and *watch* and *match*. In reading longer units they have difficulty following the line, keeping the place, and moving from one line to another. It takes these patients a long time to relearn symbol recognition and to compensate for other visual limitations, but if they are able to achieve this, reading presents no further problems for them unless there is simultaneous auditory involvement. Twenty-three per cent of the patients tested made errors in matching familiar words to pictures. Most of

these patients made even more errors when asked to point to the word spoken by the examiner, thus indicating an auditory component to the reading disability, even on a one word level.

Some patients possessed superior reading vocabulary, but still made errors grasping the meaning of sentences and simple paragraphs. This, too, appears to result from impairment of reauditorization. They recognize individual words but cannot grasp a large enough unit at one time to integrate the meaning. On paragraph material they lose the relationships necessary for comprehension because they cannot remember what has been read previously.

Reading rate is retarded even after patients comprehend with reasonable accuracy. Patients can be observed to read most of a paragraph normally, then hesitate on an individual word, rehearse it silently, perhaps with several variations, and then go back and reread in order to grasp significance.

In the author's experience, reading aloud with the patient has proved one of the most effective means of reestablishing auditory patterns and increasing reading ability. The reinforcement of auditory patterns carries over into speech as well.

In summary, reading disabilities may have visual components, but cannot usually be understood in terms of visual impairment alone.

WRITING IMPAIRMENT

This is never a pure disorder, but reflects impairment of visual functions, motor functions, and on higher levels, involves reauditorization as well. Thirty-one per cent of the patients in the group made errors copying forms and symbols. Sometimes the errors resulted from visual impairment, sometimes from motor impairment, and sometimes from both. When visual functions were impaired reversal and distortion of symbols appeared, often accompanied by evidence of spatial disorientation. When motor involvement predominated, patients had difficulty manipulating the pencil and were often able to produce only a few scratches. If occasionally a patient was able to copy a figure laboriously, perseveration appeared when a new one was attempted.

To test revisualization patients were asked to draw a man, a house, and a wheel. Some patients produced adequate representations of inanimate objects, but their human figures showed gross distortions, reflecting impairment of body scheme.

Eighty per cent of patients tested made errors spelling words ranging from first to sixth grade level. It was obvious that spelling impairment stemmed from a combination of disabilities, and that difficulty both in revisualizing symbols and in reauditorizing words and letter sequences was operating. Even here, however, it was frequently possible to differentiate by the kinds of errors produced. Patients impaired in revisualization were often unable to produce anything at all, or produced only the initial letters of a word. Reversal and distortion of letter forms appeared, and confusion such as *m* for *n*, *u* for *w*, and *b* for *f* observed. Subjects wrote upper case letters for lower and vice

versa, sometimes reporting that they knew that this was wrong, but could not "see" the one they wanted. They traced letters in the air, using movement pattern to aid impaired visual memory. They could often spell words aloud or recognize words spelled aloud easier than they could write them.

Ninety-two per cent of the patients made errors writing phrases to dictation. Errors increased as length of phrase was increased, pointing to impairment of reauditorization. When the ability to write single words exceeds the ability to write phrases or sentences employing words of no greater difficulty, impairment of reauditorization rather than of revisualization may be considered the retarding factor.

Spontaneous writing involves not only motor skills, revisualization, and reauditorization, but also the ability to evoke the desired words and retain them long enough to arrange them in meaningful sequences. The aphasic patient tends to write as he talks. The kinds of errors made are the means of identifying the underlying disabilities.

CONCEPTUAL IMPAIRMENT

Conceptual impairment is a rather vague term. It is used here to indicate certain performances involving numerical relationships, arithmetic processes, categorizing, and spatial and temporal arrangements in which aphasic patients are usually impaired. These performances must be analyzed qualitatively and are only meaningful in terms of specific underlying disabilities which they reveal. If we use simple arithmetic processes for an example, we may find that one patient fails because hemianopsia causes him to be unaware of digits in certain positions on the page. Another may not be able to work with digits in correct order or set them down in correct positions because of spatial disorientation. Another may revisualize inaccurately and write 9 for 6, 7 for 2, or 8 for 3. Others cannot evoke the auditory patterns by which most individuals recall the learned combinations used in adding, subtracting, multiplying, or dividing. Another may have retained these, but not have enough language to think through the sequences of operations necessary for problem-solving. Therapy must be directed towards overcoming or compensating for whatever basic disability is present.

Performance tests of various kinds merely serve to give the examiner a larger sample of behavior to observe and analyze. They reflect specific disabilities and give an indication of the general level of performance of which a patient is capable. This is useful, particularly when the patient cannot talk, but such tests do not constitute valid measures of intelligence for aphasic patients.

DISCUSSION

In spite of the fact that no pure disorders are found in terms of the various language functions which can be tested, aphasic patients may be grouped in three general categories, namely, 1) the severely damaged patient, 2) the most commonly observed aphasic syndrome, and 3) the same aphasic syndrome with accompanying complications interfering with language.

The severely damaged patient. This is one of the most important groups, since it invariably carries a poor prognosis and warrants identification to avoid a large amount of fruitless effort. Test patterns for patients in this group show two consistent findings. First, there is a relatively straight-line profile showing severe impairment in all language functions. Secondly, patients make errors pointing to common objects named by the examiner. This simple test is in itself a reliable index to recovery[1] if administered when physiologic conditions have stabilized and before the patient has been exposed to therapy. Its significance probably derives from the fact that it reflects damage to receptive processes basic to language functions with considerable sensitivity.

Twenty-three per cent of all patients seen in the Minneapolis Veterans Administration Hospital (an unscreened and unselected group) have come under this category. None recovered functional speech, even with intensive therapy carried on for as long as six months. It is not known, of course, what would be the result of therapy carried on over a period of years. In some cases a member of the family was trained to work with the patient. These patients were followed outside the hospital for another year without significant changes until further cerebrovascular accidents intervened.

Some of these patients appeared alert, well-oriented, well-motivated, and socially adequate. Some had previously possessed superior intelligence. They improved in ability to understand spoken language. Motor function improved. Some learned to repeat and to produce automatic responses to language stimulation. Some reactive speech appeared. These responses sometimes appeared to be of a high level but they were not voluntary. They occurred by chance and did not become stabilized with any amount of reinforcement. The patient still could not ask for a glass of water when he wanted it. Some learned to recognize a few printed words, to write their names, or to copy beautifully, but were unable to express their needs through writing as through speech.

It is considered beneficial for such patients to have a limited period of therapy if it can be obtained without sacrifice. In the first place, the reassurance which comes from the fact that the clinician understands what has happened and can communicate with the patient mitigates the initial panic and feeling of isolation and restores emotional equilibrium. Withdrawal tendencies and resulting depressions can be averted or decreased in intensity. It is desirable for members of the patient's family to participate in therapy, so that the patient and family learn to communicate with each other more adequately, and better understanding and adjustments are made possible.

It is necessary to discriminate between patients in this group and others who may have no intelligible speech but, because comprehension is impaired less severely, may eventually recover language.

The most commonly observed aphasic syndrome. Most aphasic patients, when carefully studied, present a fairly consistent clinical picture, even though they may appear to have striking differences depending upon the severity of involvement of various language functions. Careful analysis of the findings for this group indicates that the basic impairment is in reauditorization.

In the auditory area there is preserved word recognition, with increasing difficulty understanding what is said as language units increase in length.

The patient may be able to produce only jargon initially. Those less severely involved may have some usable speech, but vocabulary will be limited and expression vague. Most patients will show inconsistencies in pronunciation, paraphasia, and responses which appear confused. Struggle behavior similar to that observed in stuttering may occur when patient is frustrated in the attempt to evoke a desired word. Some patients may converse very well on a simple level, and only have difficulty when fatigued or anxious, or tested at a high level.

In reading, these patients have relatively good word recognition but have trouble comprehending longer materials. In writing, some ability to spell is usually preserved or emerges fairly rapidly. Ability to write single words exceeds ability to write sentences employing the same words. Spontaneous writing reflects word-finding and formulation difficulties.

On performance tests manipulative ability usually exceeds language ability. The patient may fail, however, because he has difficulty grasping or retaining directions or formulating the task to himself.

Prognosis for this group is good. Therapy is essential unless the following conditions obtain: 1) recovery of language occurs spontaneously in the first few days following the onset, 2) progresses so fast that observable gains are made each day, or 3) is sufficient to allow the patient to resume former occupations to the extent that he is physically able to do so. Patients who do not receive therapy commonly retain unneccessary limitations and readjust on a lower level of performance than would be required. Controlled auditory stimulation is the basis of therapy.

Additional complications. Not uncommonly the classic aphasic picture described above is complicated by associated disabilities which confuse the clinical picture and influence the patient's response to therapy. The coexisting disabilities which most frequently need to be taken into account are visual involvement, motor involvement affecting the peripheral speech mechanism, and impaired mentation.

The patient with visual impairment superimposed upon aphasia makes good progress in speech, but reading and writing disabilities are more stubborn and resistant than otherwise. Patients may succeed in reacquiring some skills, but rate of performance will probably always be somewhat retarded and the patient may never reach his former level of functioning. He should usually be counselled against setting educational or occupational goals which require proficiency in these areas.

When there is severe involvement of the peripheral speech mechanisms, the basic aphasic pattern is difficult to recognize initially because the patient can respond so little. It may become recognizable only after the patient has begun to regain speech. Training with these patients must begin with exercises for obtaining control of the musculature, and sometimes relearning to form each speech sound. As soon as the patient is able to repeat even a single

sound, repetition rather than imitation should be used. Repetition of words, phrases, and sentences should be introduced as rapidly as possible, for without the use of auditory stimulation speech will always remain labored and artificial and vocabulary limited. Patients in this group commonly acquire enough speech to communicate basic needs. The degree of normalcy obtained varies from patient to patient. It appears to be more closely related to the extent of aphasic involvement coexisting with the motor defect than to the severity of the motor defect itself.

When there is generalized brain damage with intellectual deterioration, language defects are more resistive to therapy. Specific disabilities may improve, but motivation is usually low and judgment poor. Frequently, the patient appears to respond well to a specific task, but there is no retention from one day to another. Therapy should be discontinued when it is ascertained that no consistent progress is possible. These patients are not usually critical of their own performance, and if anxiety is present it is more commonly attached to an aspect of the situation which restricts movement or produces physical discomfort. Accordingly, they are readily diverted to other activities, and discontinuing therapy is not traumatic.

SUMMARY

Examination of 65 aphasic patients revealed involvement of all language functions for each patient. However, most symptoms could be traced back to underlying auditory, visual, or motor impairment. Although individual responses were variable, a consistent clinical picture which remained stable was obtained for each patient. Patterns of impairment which tended to recur were: 1) a pattern of severe damage, 2) a consistent pattern of aphasic disabilities found in all patients, and 3) the same pattern, complicated by superimposed visual involvement, motor involvement, or mental deterioration.

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Cystometry: Its Neurologic Diagnostic Implication

Reed M. Nesbit, M.D. and William C. Baum, M.D.

On January 18, 1951, a 43 year old janitor presented himself to the urology clinic of the University Hospital for diagnosis. A lifetime of good health had been insidiously and progressively disturbed by two years of obstructive uropathy characterized mainly by decrease in the size and force of the urinary stream. On physical examination the patient was found free from pertinent abnormalities. His prostate gland was not enlarged. The urethra was calibrated through F-24 with ease. There was no neurologic deficit. On observation, however, his micturitional efforts were characterized by hesitancy and a dribbling stream, and catheterization after voiding showed 800 cc. of residual urine. This led to a thorough urologic investigation, the results of which were apparently contradictory. Here was a patient with an adequate vesical outlet, no visual endoscopic evidence of obstruction in the urethra, yet a large capacity adynamic bladder, patulous ureteral orifices, bilateral ureteral reflux of radiopaque medium introduced into the bladder on cystogram, bilateral hydroureter and hydronephrosis (figure 1), and a moderate reduction in total renal tubular function by excretory tests. A cystometric examination was done (figure 2). Enteroceptive and proprioceptive modalities were intact. The bladder was of large capacity and almost completely devoid of detrusor muscle tone. There was no evidence of response on voluntary micturitional effort, except that induced by the pressure of abdominal straining. A tentative diagnosis of vesical motor paralysis was made, and a lesion involving the ventral roots of the sacral cord predicted. Yet, this cystometric diagnosis appeared tenuous, for careful neurologic examination failed to disclose any significant abnormalities except hypoactive reflexes in the lower extremities and questionable weakness of the tibialis anterior and extensor of the great toe on the right. The consulting neurologist concluded his examination with the statement: "I can find no definite convincing neurologic abnormality, but in view of the cystometric findings would suggest lumbosacral spine films and a myelogram." These studies were made, and interestingly enough, a

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Read in the symposium on the neurogenic bladder before the Section on Urology at the 102nd meeting of the American Medical Association, New York City, June 3, 1953.

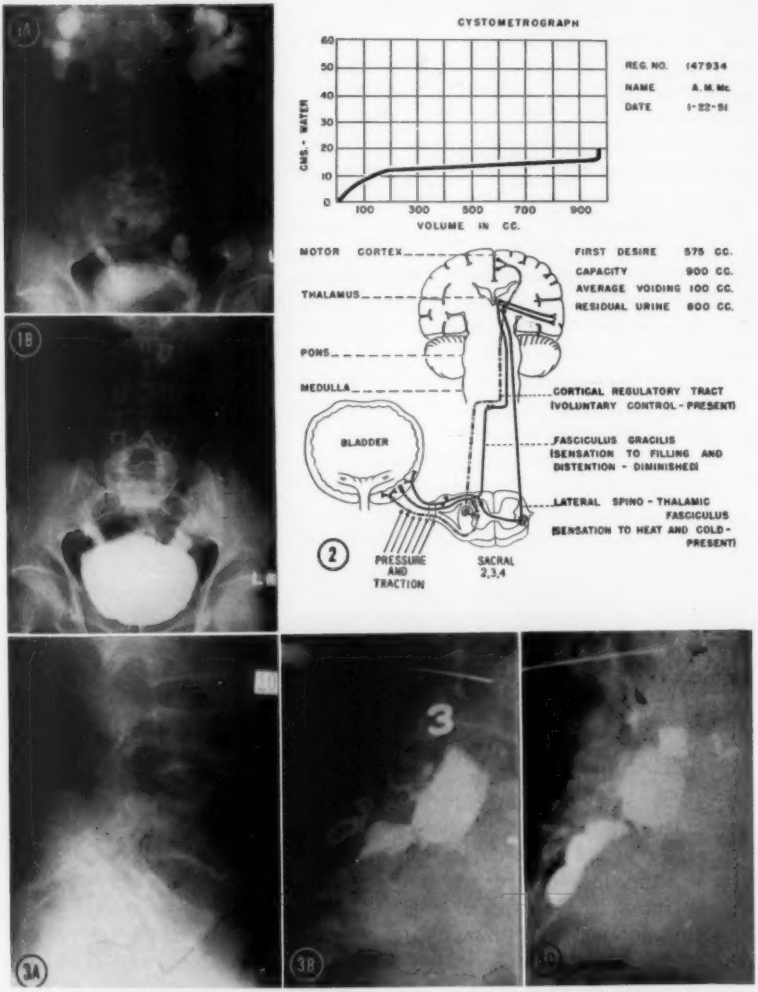


FIG. 1. *A.* Pyelogram showing hydronephrosis secondary to a motor paralytic bladder. *B.* Cystogram showing bilateral ureteral reflux through an incompetent ureterovesical junction secondary to motor paralytic bladder.

FIG. 2. Cystometrogram: Motor paralytic bladder due to traction and pressure on nerve root.

FIG. 3. *A.* Lateral view of lumbosacral spine showing spondylolisthesis. *B* and *C.* Myelogram demonstrating bizarre defect of the dural sac.

marked spondylolisthesis L-5 on S-1 was found (figure 3), unsuspected from the anteroposterior x-ray films made at the time of urography. The my-

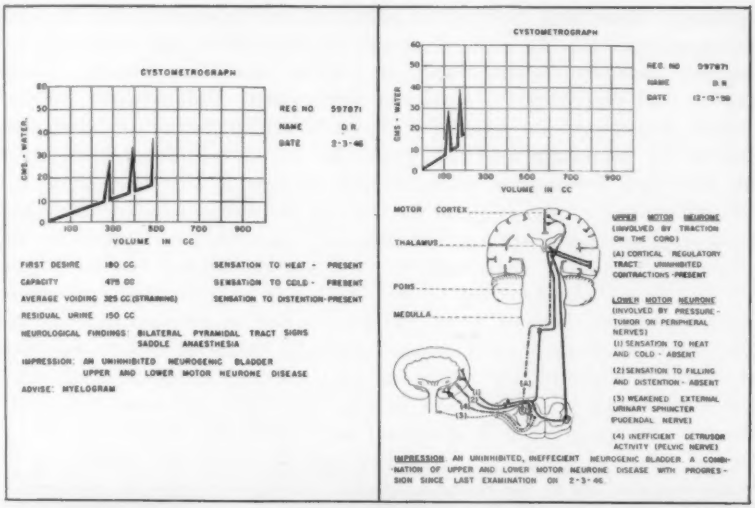
elogram demonstrated a bizarre defect with slow filling of the caudal elongation of the dural sac thought to be due to the deformity produced by the projecting bony abnormality. A laminectomy was performed and a marked constriction at the lower level of L-5 around the dura was found. Decompression was carried out and the patient, who had previously been placed on suprapubic cystotomy drainage, made an uneventful recovery, regained considerable inherent muscle tone, but to date has shown no evidence of return of true parasympathetic motor function.

It is reasonable to assume that the diagnosis in this case was first made on cystometric examination. The findings gained constituted the major evidence of neurologic abnormality that led the consultant to advise further studies of confirmatory nature. Perhaps more than anything else this example serves to keynote the major theme of this presentation, namely, that cystometry is a valuable adjunct to neurologic diagnosis, and may also serve as an index of prognostic and therapeutic significance.

There is no need to review the background of cystometry as a clinical procedure. Published reports have provided us with a neurophysiologic basis for the clinical applications demonstrated by investigators in many fields.[1–13] Despite its proven worth, there still remains a hiatus between theory and practical application to the extent that some urologists have concluded that the procedure is without merit. It is believed that such blanket rejection is unwarranted, yet there must be some real basis for this variance of opinion relative to its worth. Perhaps it is fair to say that in the majority of instances the failure to realize the value of the information gained lies more with the examiner and the nature of his interpretation rather than with any intrinsic fault in the test itself. In teaching we refer to the cystometer as a reflex hammer of bladder activity so as to orient student thinking in terms of simple neurologic concepts rather than a complex diagnostic machine.

Considerable emphasis should be placed on the fact that the curves derived from cystometry cannot themselves yield a final diagnosis like the tracings of the electroencephalogram or electrocardiogram, which may give determinative information. The cystometric curve is only part of a comprehensive study and must be interpreted in context. It cannot be divorced from a complete survey of the patient, nor can it be separated from the vagaries introduced by the experience of the individual examiner. For instance, the inexperienced examiner may easily interpret excessive respiratory excursions in an excitable patient as indicative of uninhibited vesical activity, when in reality it is but the reflection of changes in intraabdominal pressure induced by diaphragmatic activity. Or he may, on asking the patient to void, ascribe an increase in pressure reflected on the tracing to real detrusor activity, when careful observation would disclose it to be due to voluntary abdominal muscular effort. These difficulties are not insurmountable, but introduce a personal element that must be taken into account.

The common origins of disease often require the specialist to take into consideration clinical aspects of the problem beyond his own narrow field.


CYSTOMETROGRAPH
CMS - WATER
VOLUME IN CC
REG. NO 597871
NAME D.R.
DATE 2-3-46
FIRST DESIRE 180 CC
CAPACITY 475 CC
AVERAGE VOIDING 325 CC (STRAINING)
RESIDUAL URINE 150 CC
SENSATION TO HEAT - PRESENT
SENSATION TO COLD - PRESENT
SENSATION TO DISTENTION - PRESENT
NEUROLOGICAL FINDINGS: BILATERAL PYRAMIDAL TRACT SIGNS
SADDLE ANAESTHESIA
IMPRESSION: AN UNINHIBITED NEUROGENIC BLADDER
UPPER AND LOWER MOTOR NEURONE DISEASE
ADVISE: MYELOGRAM
CYSTOMETROGRAPH
REG. NO 597871
NAME D.R.
DATE 12-13-'50
MOTOR CORTEX
THALAMUS
PONS
MEDULLA
UPPER MOTOR NEURONE
(INVOLVED BY TRACTION ON THE CORD)
(A) CORTICAL REGULATORY TRACT: UNINHIBITED CONTRACTIONS - PRESENT
LOWER MOTOR NEURONE
(INVOLVED BY PRESSURE - TUMOR ON PERIPHERAL NERVES)
(1) SENSATION TO HEAT AND COLD - ABSENT
(2) SENSATION TO FILLING AND DISTENTION - ABSENT
(3) WEAKENED EXTERNAL URINARY SPHINCTER (PUDENDAL NERVE)
(4) INEFFICIENT DETRUSOR ACTIVITY (PELVIC NERVE)
IMPRESSION: AN UNINHIBITED, INEFFECIENT NEUROGENIC BLADDER A COMBINATION OF UPPER AND LOWER MOTOR NEURONE DISEASE WITH PROGRESSION SINCE LAST EXAMINATION ON 2-3-46.

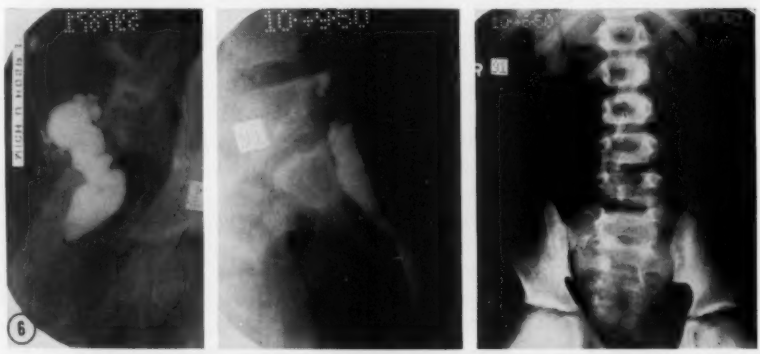


FIG. 4. *(above left)* Cystometrogram: Uninhibited neurogenic bladder associated with evidences of upper and lower motor neurone involvement (1946).
FIG. 5. *(above right)* Cystometrogram: Uninhibited neurogenic bladder with increase in neurologic abnormality (1950).
FIG. 6. Spine film demonstrating spina bifida. Myelogram showing deformity of dural sac in mid-sacral region.

The investigating urologist is lost if he is unaware of the clinical neurologic implications of his cystometric findings, and, of course, the neurologist or neurosurgeon must be cognizant of the urologic significance of the interpretation as well. The necessity for combined effort used to advantage is well illustrated by the following case: A boy of ten, admitted for investigation of enuresis and stress incontinence, was found on physical examination to have bilateral pyramidal tract signs, saddle anesthesia, and a patulous anal

sphincter. Spine films disclosed an anomalous development of S-1. A cystometric examination (figure 4) demonstrated uninhibited vesical activity, apparently inefficient, in that significant residual urine was present. Enteroceptive and proprioceptive sensations were intact. Unfortunately, circumstances necessitated the patient's discharge before completion of his studies, and he did not return until four years later for reevaluation. At that time his neurologic examination disclosed some increase in long tract signs, but was otherwise unchanged. From the urologic standpoint, however, there had been progression of symptoms with increasing incontinence. Cystometric examination disclosed a small capacity, inefficient uninhibited bladder (figure 5), with the additional findings of complete loss of proprioceptive and enteroceptive sensation, both of which had been intact on previous examination. Cystoscopy disclosed a weak external muscular sphincter and no evidence of vesical neck obstruction. Here was an interesting combination of upper and lower motor neurone disease, that is, both long tract signs and saddle changes. The progression of symptoms and cystometric evidence of the increased extent of involvement including loss of sensory and partial loss of motor function led to the recommendation that myelography be performed. X-ray examination by this technic disclosed a narrowing and curvature of the dural sac in the midsacral area (figure 6). A space-occupying lesion with local sacral damage and traction on the cord with attendant pyramidal tract signs was predicted. Laminectomy was advised and carried out. An obvious developmental defect of the posterior arc of S-1 and S-2 was noted. On removal of the laminae a large lipoma was discovered continuous through the dura with a similar mass over the cauda equina. The tumor was obviously exerting considerable traction on nerve structures. Its removal was effected without further incident. The cystometric examinations did much both to substantiate the extent and indicate the progress of this lesion, and were, on the whole, an integral part of the evaluation that led to the choice of operation, substantiation of diagnosis, and indicated therapy.

It would seem logical from the foregoing discussion to conclude that this urologic approach to neurologic investigation gives considerable information to the examiner who suspects disease of the lumbosacral cord and its cortical or subcortical connections. From the practical standpoint the physician may question the technic by which information was obtained in these two cases. Fortunately, both the equipment necessary and method used have the advantage of simplicity. These advantages may be augmented by an orderly method of procedure to the extent that the examiner may include the following questions in the urologic aspect of his neurologic survey, and seek their answers:

1. *Are enteroceptive sensations intact?* Vesical sensations of pain and temperature are probably mediated over both sympathetic and parasympathetic nerves, synapse in the lumbosacral segments, and are carried to thalamic levels in the lateral spinothalamic fasciculus. The continuity of this pathway may be tested by the introduction of both hot and cold water into the bladder

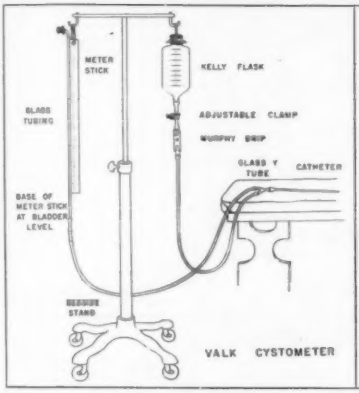


Fig. 7. The Valk cystometer.

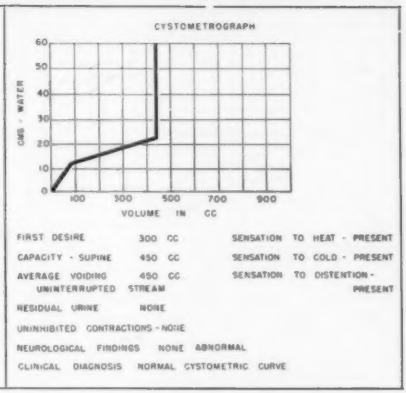


Fig. 8. The normal cystometrogram.

by way of a catheter. The normal patient will be able to differentiate between them and judge degree as well.

2. *Are proprioceptive sensations intact?* The sensations of filling, pressure, and desire to void depend on the pelvic nerves, posterior roots, and nuclei of the conus, and reach cortical levels via the fasciculus of Gracilis. The integrity of these connections may be validated by filling the bladder with progressive increments of water and noting the volume at which response is given and the degree of response. Both enteroceptive and proprioceptive sensations may obviously be interrupted at any level. It is recognized, however, that even in such a complete lesion as transverse myelitis the urge to void may be lost, but a vague sensation of fullness may remain. Like the aura before a convulsive seizure it may take many forms and is interpreted by the patient as burning pain, vague distress, and so on. It appears to be connected with the sympathetic innervation and has been thought to have origin in the reflection of the peritoneum over the bladder. In involvement of the cord above the fourth or fifth dorsal segments there usually is complete loss of the feeling of fullness in that afferent pathways from the peritoneum are involved at that level. In lesions above this segment bladder fullness is reflected by pathologic autonomic reflexes, especially in high cervical disease, characterized by profuse sweats, vasomotor instability, chilling, headache, and so on. Thus, one not only may determine the integrity of proprioceptive sensation but may gauge approximately the level of disease by the nature of the response to filling.

3. *Is the lower sacral reflex arc intact?* The nature of detrusor response to increasing amounts of water pressure reflects both the activity of smooth muscle with its inherent ability to maintain tone and resist stretch, and the integrity of the pelvic nerve whose origins lie in sacral segments 2, 3, and 4. This aspect of cystometry may be carried out with the simple Valk cystometer

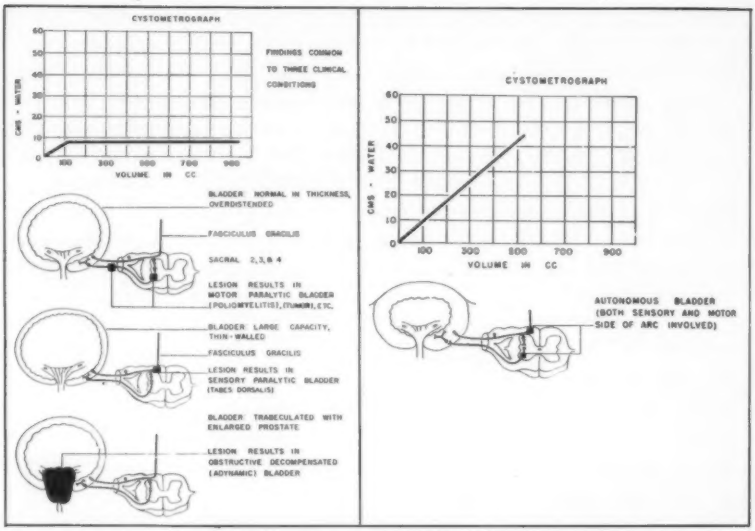

CYSTOMETROGRAPH
CMS - WATER
VOLUME IN CC
FINDINGS COMMON TO THREE CLINICAL CONDITIONS
BLADDER NORMAL IN THICKNESS, OVERDISTENDED
FASCICULUS GRACILIS
SACRAL 2, 3, & 4
LESION RESULTS IN MOTOR PARALYTIC BLADDER (POLIOMYELITIS), (TUMOR), ETC.
BLADDER LARGE CAPACITY, THIN-WALLED
FASCICULUS GRACILIS
LESION RESULTS IN SENSORY PARALYTIC BLADDER (TABES DORSALIS)
BLADDER TRABECULATED WITH ENLARGED PROSTATE
LESION RESULTS IN OBSTRUCTIVE DECOMPENSATED (ADYNAMIC) BLADDER
CYSTOMETROGRAPH
CMS - WATER
VOLUME IN CC
AUTONOMOUS BLADDER (BOTH SENSORY AND MOTOR SIDE OF ARC INVOLVED)

FIG. 9. *(left)* Three clinical entities associated with decreased or absent vesical detrusor activity.
FIG. 10 *(right)* Autonomous neurogenic bladder: Simultaneous involvement of sensory and motor divisions of the lower motor neurone reflex arc.

(figure 7) and requires no more equipment than a meter stick, glass tubing, Kelly flask, and rubber tubing. Water is allowed to pass through the system at a constant rate and elicits a characteristic response interpreted as the normal cystometric curve (figure 8). The bladder accomplishes this by constant adjustment of its musculature to the increasing volume, maintaining an intravesical pressure of from 1 to 25 cm. of water. At capacity, motor impulses mediated over the efferent limb of the lower motor neuron reflex arc cause a series of contractions increasing in amplitude until a final massive contraction occurs and the bladder empties without appreciable residual urine.

In evaluating the character of motor response on cystometry one must be cognizant of the various pathologic entities that might contribute to a decrease in or absence of detrusor activity and thus produce a similar cystometric curve. In general, three categories must be considered (figure 9): 1) a lesion involving the motor side of the lower reflex arc either at the anterior horn, as in poliomyelitis, or along the course of the pelvic nerve, as may occur with surgical trauma or involvement by metastatic neoplasm; 2) a lesion involving the sensory side of the reflex arc, however contradictory it may seem, which can, as in tabes dorsalis, so reduce the perception of vesical fullness that the patient gradually decompensates his vesical smooth muscle through chronic overdistention; and 3) an obstructive lesion of the lower urinary tract that may exist by coincidence, such as benign prostatic hypertrophy or muscular vesical neck contracture, and produce an adynamic

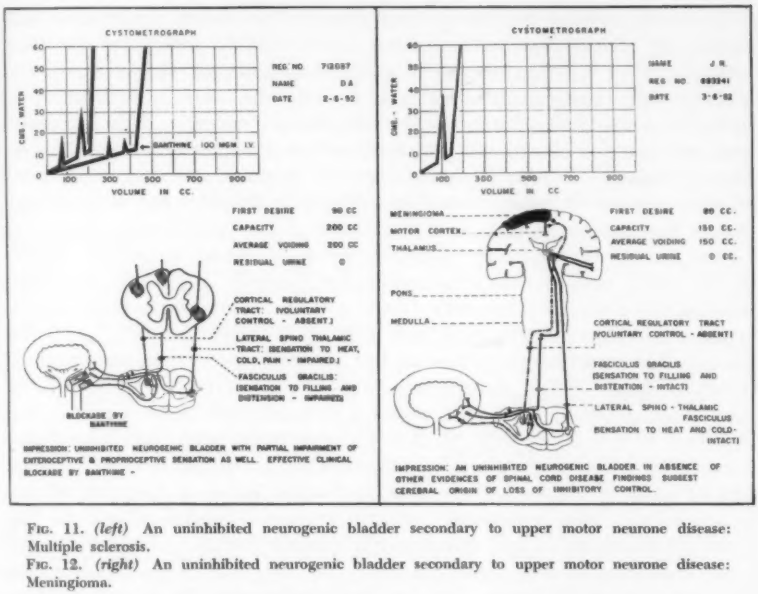

CYSTOMETROGRAPH
REG NO 712087
NAME D A
DATE 2-5-52
CMS - WATER
VOLUME IN CC.
BANTHINE 100 MGM I.V.
FIRST DESIRE 90 CC
CAPACITY 200 CC
AVERAGE VOIDING 200 CC
RESIDUAL URINE 0
CORTICAL REGULATORY TRACT: (VOLUNTARY CONTROL - ABSENT.)
LATERAL SPINO THALAMIC TRACT: (SENSATION TO HEAT, COLD, PAIN - IMPAIRED.)
FASCICULUS GRACILIS: (SENSATION TO FILLING AND DISTENSION - IMPAIRED)
BLOCKADE BY BANTHINE
IMPRESSION: UNINHIBITED NEUROGENIC BLADDER WITH PARTIAL IMPAIRMENT OF ENTEROCEPTIVE & PROPRIOCEPTIVE SENSATION AS WELL. EFFECTIVE CLINICAL BLOCKADE BY BANTHINE -
CYSTOMETROGRAPH
NAME J R.
REG NO 693241
DATE 3-6-52
CMS - WATER
VOLUME IN CC
FIRST DESIRE 80 CC.
CAPACITY 150 CC.
AVERAGE VOIDING 150 CC.
RESIDUAL URINE 0 CC.
MENINGIOMA
MOTOR CORTEX
THALAMUS
PONS
MEDULLA
CORTICAL REGULATORY TRACT (VOLUNTARY CONTROL - ABSENT)
FASCICULUS GRACILIS (SENSATION TO FILLING AND DISTENTION - INTACT)
LATERAL SPINO - THALAMIC FASCICULUS (SENSATION TO HEAT AND COLD - INTACT)
IMPRESSION: AN UNINHIBITED NEUROGENIC BLADDER IN ABSENCE OF OTHER EVIDENCES OF SPINAL CORD DISEASE FINDINGS SUGGEST CEREBRAL ORIGIN OF LOSS OF INHIBITORY CONTROL.

FIG. 11. *(left)* An uninhibited neurogenic bladder secondary to upper motor neurone disease: Multiple sclerosis.
FIG. 12. *(right)* An uninhibited neurogenic bladder secondary to upper motor neurone disease: Meningioma.

bladder. It is obvious that the burden of differentiation in these three categories should not fall entirely on the cystometric examination, but should be borne by the results of a careful history and physical examination, particularly a detailed urologic investigation including endoscopic inspection of the urethra and vesical neck. To aid in the separation of these three similar types of cystometric curves having a different etiology, they are given the respective descriptive titles of: 1) motor paralytic bladder, 2) sensory paralytic bladder, and 3) obstructive decompensated bladder.

It is possible, of course, to have both sensory and motor sides of the lower reflex arc involved simultaneously (figure 10). This occurs clinically in lesions of the cauda equina, be they congenital, traumatic, inflammatory, or neoplastic, and may occur temporarily during spinal anesthesia. It should be emphasized that such a bladder is not flaccid, as formerly thought, but as shown by Nesbit and Lapides[10] is possessed of its inherent smooth muscle tone, resists stretch, and produces a straight line cystometric curve by reason of this fact. Such a bladder is aptly termed autonomous for it is truly on its own, devoid of all nerve supply except its own inherent smooth muscle units.

Granted then that cystometry is a valuable adjunct to the neurologic evaluation of lesions of the lower reflex arc, its peripheral nerves, and cortical or subcortical connections, does it add to the investigation of upper motor neuron disease? In answer, the neurologist may ask himself the fourth question:

4. *Is the cortical regulatory tract intact?* The infant possesses a basic pattern of vesical function dependent on the simple activity of the lower reflex arc, that is, filling, sensation of fullness, desire to void, efferent motor activity, and emptying. The dictates of acceptable social micturitional behavior have made modification of this simple act a necessity. For this reason, with training and maturation the child evolves a higher center of suprasegmental inhibitory activity mediated over corticospinal pathways which exerts effective control of reflex micturition. This fact provides the clinician with one of the most important clues to disease of the corticospinal system, for interruption of this pathway invariably results in return, to various degrees, of the infant type of vesical behavior. For example, a 36 year old woman was admitted to the University Hospital with a three year history of increased frequency of urination and progressive difficulty with ambulation. Examination found her urine normal, but a cystometric evaluation (figure 11) disclosed partial loss of enteroceptive and proprioceptive sensation with numerous uninhibited contractions resulting in involuntary emptying at a small capacity. This coupled with the findings of nystagmus on right lateral gaze, a marked increase in deep tendon reflexes, clonus, positive Babinski, diminution of sense of motion and position, and ataxia led to a diagnosis of multiple sclerosis. Her cystometric examination was a helpful adjunct to diagnosis, substantiating lateral and posterior column disease and elucidating the cause of abnormal micturitional behavior. Not only that, further study proved the therapeutic value of the test, for by administering 100 mg. of Banthine, an agent causing autonomic blockade, the uninhibited contractions ceased and capacity was greatly increased. On a regime of 50 mg. of this drug four times daily the patient returned to near-normal voiding function. Such uninhibited activity may accompany any disease involving the cord, and is commonly seen in diabetic myelopathy, posterolateral sclerosis, and cord tumor.

Higher center disturbances may likewise be reflected by uninhibited bladder contractions. A 37 year old man treated with cortisone by an ophthalmologist for retrobulbar neuritis was admitted one night following a grand mal seizure. Close questioning revealed that the patient had noted headache, nausea, and an increased frequency of urination for some time prior to the start of therapy. His major admission complaint was severe low back pain. This coupled with compression of the bodies of D-6 and D-7 and a positive Babinski on the left with no other localizing signs led to the suspicion that he had sustained cord damage following a convulsive seizure. A cystometric examination was performed (figure 12) and an uninhibited neurogenic bladder found. However, proprioceptive and enteroceptive sensations were perfectly normal. This fact led the examiner to suspect that the release of inhibitory control had its origin in the cortex and probably not in the cord. Subsequent investigation by electroencephalography and percutaneous arteriography proved this impression correct, for a space-occupying lesion was discovered in the anterior quadrant. A craniotomy was done, with successful removal of a meningioma and a return of the individual to normal.

CONCLUSION

Cystometry may be likened to a reflex hammer applicable to the diagnosis of neurologic or neurosurgical entities whose presence is made evident by disturbances of vesical function. It is a diagnostic tool possessed of the advantages of simplicity of construction and ease of performance. Admittedly experience is a prerequisite to interpretation, but this should prove no barrier to the interested physician. The acquisition of knowledge of diagnostic, therapeutic, and prognostic significance is ample reward for proficiency in its use.

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Bodily fatigue is another exciting cause of megrim, and especially any violent effort or sudden exertion. When speaking of the value of exercise as a remedial agency, I pointed out the precautions which are necessary in this respect. Where manual labour is a means of livelihood, it is for the most part limited by the customary and regular hours of work, but this is not the case with much of that domestic labour which falls to the lot of many women of the poorer class who are often worked beyond their strength and in a very irregular way; here it is easy to discern but difficult to apply the remedy. Standing about is a form of bodily exertion to which many are liable whose business it is to overlook the labour of others, and though it counts for little, and is very apt to be indefinitely prolonged under a pressure of business, it is about as exhausting a form of labour as any with which I am acquainted, and patients may require to be cautioned on the subject. "To avoid excessive exertion after fatigue," says Prof. Lebert, "and to take proper rest after such fatigue, are often the best preservatives against Migräne."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Agenesis of the Corpus Callosum

A Study of 18 Cases Diagnosed During Life

Malcolm B. Carpenter, M.D.

ROENTGEN CRITERIA for the diagnosis of agenesis of the corpus callosum during life were established independently by Davidoff and Dyke[1] and Penfield and Hyndman[2] in 1934. Reviews of the literature[3,4] reveal that intravitam diagnosis of this anomaly was made in at least 47 cases by encephalography; seven cases in which encephalograms were done have been confirmed at autopsy. Also in the literature are a few scattered reports[5,6,7] of "bizarre" encephalograms presenting features characteristic of agenesis of the corpus callosum but with other diagnoses. In institutions where large series of encephalograms have been performed this anomaly has been recognized in as high as 3 per cent of the cases.[3,8] As far as can be determined all intravitam diagnoses were made by encephalography or surgical exploration.[9,10,11,12]

The present study is based on 19 cases of agenesis of the corpus callosum, of which all but one were diagnosed during life at the Neurological Institute and Babies Hospital, New York City, between 1933 and 1953. Analysis of these cases presented data differing in some respects from that recorded in the literature and were considered noteworthy. With the exception of the first three (reported by Davidoff and Dyke[1]), none of these cases has been previously reported. Two of the 19 came to autopsy and confirmed the clinical (roentgen) diagnosis.

CLINICAL DATA

No significant sexual distribution was apparent in the patients of this series; there were nine females and ten males. Birth was described as normal in 11 cases, while definite birth trauma (precipitous labor, protracted labor, and traumatic breech delivery) was reported in three patients. Two patients had been delivered by cesarean section; in case 13 cesarean section was considered necessary because prenatal roentgenograms disclosed abnormal cephalic enlargement. Details concerning birth were lacking in three cases.

Initial symptoms became apparent shortly after birth and prior to three years of age in 17 cases. In the other two cases initial symptoms appeared at 16 and 23 years of age. Jacksonian or focal seizures initiated symptomatol-

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ogy in seven cases; physical and mental retardation were reported as the first symptoms in six cases; and progressive increase in head size was the first apparent abnormality in the remaining six patients. Subsequent symptoms consisted of convulsive disorders in five cases, physical and mental retardation in five cases, hemiparesis in three cases, amaurosis in two cases, indistinct speech in two cases, and increasing head size in two cases (table 1).

Twelve patients had verified major seizures, which in nine cases were either focal or Jacksonian. Combined major and minor (psychomotor) seizures occurred in only one patient (case 7). Seizures began prior to three years of age in nine patients, and at 16 and 23 years of age in two other cases. In three patients postictal paresis ultimately became permanent. Initial convulsive episodes were associated with hyperpyrexia in three cases; one of these patients had acute encephalitis. Alternating unilateral seizures associated with fever occurred in case 18. Predominantly nocturnal seizures were described in four cases, and status epilepticus occurred in three patients. Increasing frequency and severity of seizures with age were reported in seven patients.

Physical retardation was judged to be present in ten cases because of delays in motor development and acquisition of simple skills (for example, holding the head erect, sitting, standing, walking, and talking). Bowel and bladder training were more difficult and usually were not completed until older ages. Case 9 was unable to feed herself or walk unaided at three and a half years. Another patient did not stand unassisted until age four and first walked at eight years. The degrees of physical retardation were highly variable and comparisons between individual patients were difficult.

Psychometric studies were performed on 15 patients and included such tests as the Stanford-Binet, Merrill-Palmer, Kuhlmann-Binet, Cattell Infant Intelligence, Pintner-Patterson, Terman, Goodenough, Arthur, Porteus Mazes, Gesell Mental Schedule, and the Wechsler-Bellevue. Twelve of the tested patients were found to be mentally retarded or mentally defective. The remaining three patients were judged to be of average intelligence. Three patients were tested at older ages and the results confirmed initial testing; no obvious deterioration was detectable in the scores of two patients tested ten years later. Psychometric data is recorded in table 2.

Eight patients were hydrocephalic. This condition was suspected prior to birth in one case and was obvious soon after birth in six cases; in another case it was not apparent until about one year. Hydrocephalus was nonobstructive and associated with severe mental and physical retardation in all cases and with optic atrophy in three patients. Only three of the hydrocephalic patients had convulsive disorders.

The general physical examination was within normal limits in six patients. Pertinent findings in the other cases included hydrocephalus in eight cases; ocular hypertelorism in two; and calcaneovalgus foot deformity, cleft palate, bilateral cryptorchidism, and microcephaly in single cases. Neurologic examination was reported as normal in eight patients. Positive findings in the other cases included hemiparesis of varying degrees in four cases; ataxic gait

TABLE 1
SUMMARY OF 19 CASES OF AGENESIS OF THE CORPUS CALLOSUM

Case No.	Year Diagnosed	Hospital No.	Sex	Age		Symptoms		Findings		Comment
				Onset of symptoms	Diagnosis	Initial	Subsequent	General physical	Neurologic	
1	1933	16591	F	2 yrs.	6 yrs.	Focal seizures	Left hemiparesis	Premature puberty	Left hemiparesis	Birth history not available; autopsy
2	1933	15891	F	2.5 yrs.	3 yrs.	Retarded mental and physical development	Jacksonian seizures	Normal	Normal	Birth normal
3	1933	17548	M	16 yrs.	21 yrs.	Jacksonian seizures	Weakness left leg	Normal	Paresis left lower extremity, hesitant speech	No birth history available
4	1935	449856	F	3 yrs.	11 yrs.	Retarded mental and physical development	Generalized seizures	Facial asymmetry	Ataxic gait	Birth normal
5	1936	27316	M	2 yrs.	6 yrs.	Jacksonian seizures	Amaurosis, ataxic gait, indistinct speech	Normal	Bilateral optic atrophy, dysarthria, ataxic gait	Birth normal
6	1936	27790	M	23 yrs.	24 yrs.	Jacksonian seizures	Same as initial	Normal	Normal	No birth history available
7	1936	30297	F	14 mos.	12.5 yrs.	Retarded mental and physical development	Major and minor seizures	Thoracic kyphosis and scoliosis	Hemiatrophy left extremities	Birth normal
8	1936	31147	M	2.5 yrs.	5.5 yrs.	Focal seizures	Left spastic hemiparesis	Normal	Left spastic hemiparesis	Protracted labor
9	1940	602970	F	1 yr.	3.5 yrs.	Progressive increase in head size	Retarded physical and mental development	Hydrocephalus	Ataxic gait, bilateral deafness, generalized hypotonia	Birth normal
10	1940	614801	M	birth	6 mos.	Progressive increase in head size	Retarded physical and mental development	Hydrocephalus	Bilateral blindness	Birth normal, operation, autopsy
11	1941	660371	M	birth	7.5 mos.	Unable to hold head up	Physical and mental retardation	Hydrocephalus	Normal	Birth normal (breech delivery)
12	1942	672076	M	birth	5.5 yrs.	Retarded physical and mental development	Spastic diplegia	Microcephalia	Spastic diplegia	Birth normal (?)
13	1943	720659	M	birth	11 mos.	Progressive increase in head size	Focal seizures	Hydrocephalus, ocular hypertelorism	Bilateral optic atrophy	Cesarean section
14	1949	980189	M	3 yrs.	7 yrs.	Physical and mental retardation	Slurred speech	Bilateral cryptorchidism	Normal	Cesarean section
15	1949	972510	F	6 wks.	9 mos.	Progressive increase in head size	Generalized seizures, amaurosis, physical and mental retardation	Hydrocephalus	Bilateral optic atrophy	Traumatic birth (breech—fracture right femur)
16	1950	983680	F	4 mos.	4 mos.	Jacksonian seizures	Same as initial	Normal	Normal	Birth normal
17	1950	011760	F	birth	6 wks.	Progressive increase in head size	Physical and mental retardation	Hydrocephalus, cleft palate	Normal	Precipitous labor
18	1951	050236	F	7 mos.	18 mos.	Focal seizures	Mental retardation	Hydrocephalus, ocular hypertelorism, bilateral calcaneovalgus foot deformity	Normal	Birth normal
19	1953	131451	M	birth	18 mos.	Physical and mental retardation	Increasing head size	Hydrocephalus	Normal	Birth normal, craniostenosis

TABLE 2

PSYCHOMETRIC DATA ON 15 PATIENTS WITH AGENESIS OF THE CORPUS CALLOSUM

Case No.	Chronologic age Years	Chronologic age Months	Mental age Years	Mental age Months	Test	Estimated I. Q.
1	3	6	3	8	Terman	105
	6	1	6	6	Terman	107
			6	3	Merrill-Palmer	
2	3	5	2	3	Kuhlmann-Binet	69
			1	11	Merrill-Palmer	
3	21	9	11	3	Terman	70
			8	6	Pintner-Patterson	
			11	0	Porteus Mazes	
4	11	8	3	6	Stanford-Binet	
			3	6	Merrill-Palmer	
5	6	6	5	4	Stanford-Binet	82
			4	11	Merrill-Palmer	
			5	6	Goodenough	
7	12	8	8	2	Stanford-Binet	64
			7	6	Goodenough	
	22	0			Wechsler-Bellevue	67
			7	6	Goodenough	
8	5	5	5	6	Stanford-Binet	102
			6	3	Pintner-Patterson	
			4	2	Merrill-Palmer	
			6	3	Goodenough	
	9	11	9	10	Stanford-Binet	99
			10	5	Arthur	105
			10	0	Goodenough	
	19	11			Wechsler-Bellevue	102
9	3	6	1	6	Kuhlmann-Binet	
			1	3	Gesell Mental Schedule	
10	0	6	0	3	Kuhlmann-Binet	
			0	3	Gesell Mental Schedule	
11	1	1	0	5–7	Gesell Mental Schedule	
13	0	11	0	7	Kuhlmann-Binet	
			0	8	Cattell	
			0	7	Gesell Mental Schedule	
14	7	2	5	3	Stanford-Binet	72
			5	1	Merrill-Palmer	
15	0	9	0	3-4	Gesell Mental Schedule	
18	1	6	0	8	Gesell Mental Schedule	

in three; bilateral optic atrophy in three; and deafness, anosmia, spastic diplegia, and homonymous hemianopsia in individual patients. A summary of the findings is recorded in table 1. Speech impairment was noted in five patients and consisted primarily of dysarthria, except for case 9 who had not

learned to speak at ten years of age but was considered to comprehend simple commands.

Electroencephalograms were made on only seven patients of this series (early cases were lacking these data). No distinctive encephalographic pattern was apparent for the group. Slow wave foci were found in the parietal and temporal regions in four patients and asymmetric activity of low voltage was reported once. None of these cases presented the striking dyssynchrony in the occipital region reported by Goldensohn, Clardy, and Levine[13] and Bunts and Chaffee.[14] One record was considered to be within normal limits.

Analysis of the cerebrospinal fluid did not reveal significant findings. Spinal fluid protein was below 37 mg. per cent in all but one case, and a traumatic tap prevented reliable estimation in that case. Spinal fluid serologies and colloidal gold curves were negative.

ENCEPHALOGRAPHIC STUDIES

Pneumoencephalograms were performed on 12 patients of this series, ventriculograms on four patients, and both pneumoencephalograms and ventriculograms on three patients. In those cases subjected to both procedures, pneumoencephalography was usually done first and proved to be unsatisfactory. Encephalographic findings are summarized in table 3. The principal findings conform to the criteria established by Davidoff and Dyke, but not all of the criteria were found in each case. The five most common encephalographic features in order of frequency were: 1) dorsal extension and dilatation of the third ventricle, 2) wide separation of the lateral ventricles, 3) angular dorsal margins of the lateral ventricles (bat-wing appearance), 4) elongation of the interventricular foramina, and 5) dilatation of the posterior horns of the lateral ventricles.

TABLE 3

PNEUMOENCEPHALOGRAPHIC FINDINGS IN 19 CASES OF AGENESIS OF THE CORPUS CALLOSUM

Findings	*No. of Cases*
Wide separation of the lateral ventricles	18
Angular dorsal margins of the lateral ventricles (bat-wing appearance)	13
Concave mesial borders of the lateral ventricles	7
Dilatation of the posterior horns of the lateral ventricles	10
Elongation of the interventricular foramina	11
Dorsal extension and dilatation of the third ventricle	18
Radial arrangement of sulci on medial surface of hemisphere	7
Hydrocephalus	8
Dilatation of cerebral subarachnoid spaces, diffuse (cortical atrophy)	4

Hyndman and Penfield[9] and Pospiech[8] distinguished between complete and partial agenesis of the corpus callosum on the basis of encephalographic data. Dorsal extension of the caudal portion of the third ventricle above the level of the lateral ventricles (in the lateral projection) was said to indicate

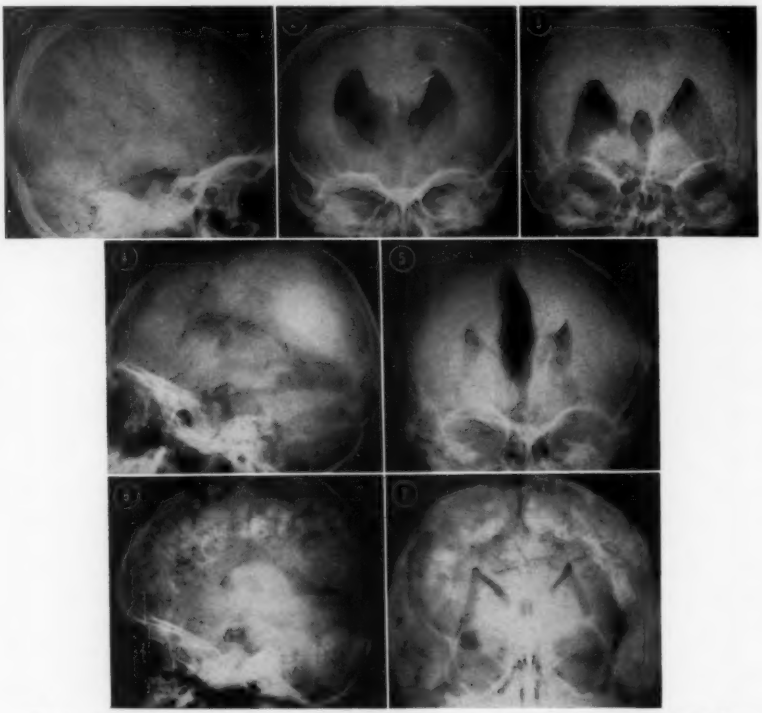


FIG. 1. *Case 5.* Lateral view of pneumoencephalogram demonstrating radial arrangement of the sulci on the medial aspect of the hemispheres, but without filling of the ventricular system.

FIG. 2. *Case 5.* Anteroposterior view of ventriculogram showing dilatation of the lateral and third ventricles with marked concave mesial margins of the lateral ventricles.

FIG. 3. *Case 6.* Anteroposterior view of pneumoencephalogram revealing widely separated, dilated lateral ventricles, angular dorsal margins of the lateral ventricles, and dilatation and dorsal extension of the third ventricle.

FIGS. 4 and 5. *Case 8.* Lateral and anteroposterior views of pneumoencephalogram showing tremendous dilatation and dorsal extension of the third ventricle, dilatation of the posterior horns of the lateral ventricles, wide separation and angular dorsal margins of the lateral ventricles, and elongation of the interventricular foramina.

FIGS. 6 and 7. *Case 9.* Lateral and anteroposterior views of pneumoencephalogram showing radial arrangement of the sulci on the medial surface of the hemispheres, wide separation of the lateral ventricles, and angular dorsal margins of the lateral ventricles.

partial agenesis of the corpus callosum, because the rudimentary or partially formed rostrum and body prevented dorsal displacement of the anterior part of the third ventricle. It is to be remembered that the corpus callosum develops in a rostrocaudal fashion so that in partial agenesis of this structure it is usually the splenium and posterior portion of the corpus that are lacking or attenuated. When the rostral portion of the third ventricle is dorsally displaced between the lateral ventricles, the corpus callosum is usually com-

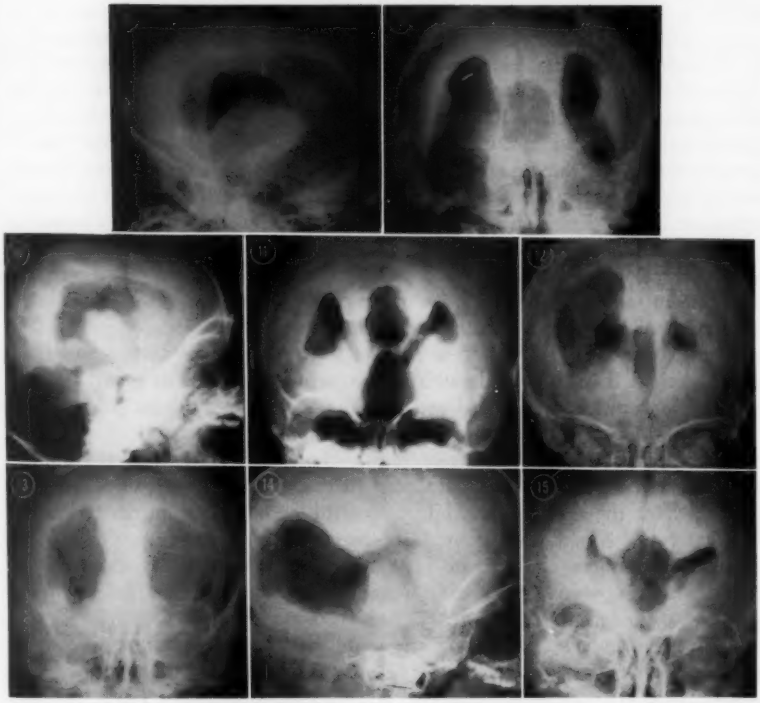
pletely absent. These encephalographic observations were confirmed by autopsy in two cases reported by Pospiech. On this basis it was felt that 18 of the cases considered here represented complete agenesis of the corpus callosum. In case 4 the third ventricle was not adequately visualized, thus making it impossible to judge whether agenesis was complete or partial. A notching of the third ventricle noted in case 16 was thought to have been produced by the falx cerebri. Although porencephalic cysts are not an uncommon associated finding in this condition, such a cyst was found in only one instance (case 18).

Pathologic confirmation of the encephalographic diagnosis was obtained in two of the 19 cases. The first case, considered originally to have a cyst of the cavum septi pellucidi, was subjected to operation, but the true nature of the condition was not revealed until autopsy. The corpus callosum was completely absent and a thin greyish translucent membrane was found covering the third ventricle. The fornices were present, the choroid plexus attenuated, and the gyri on the medial aspect of the frontal and parietal lobes abnormally developed. This case originally reported by Davidoff and Dyke provided the initial encephalographic criteria for the diagnosis of this condition during life. In case 10 an attempt was made to treat the associated hydrocephalus by cauterization of the choroid plexus, but the patient died during the procedure. Autopsy disclosed complete agenesis of the corpus callosum, incomplete fusion of the neural tube at the level of the aqueduct of Sylvius, and heterotopic cortical tissue in the island of Reil (right) and the walls of the lateral ventricles. The septum pellucidi and the fornices were present. One other (case 2) was explored for what was thought to be a cyst of the cavum septi pellucidi, but the region of the corpus callosum was never visualized because an anomalous cortical vein (stated to be as large as the child's carotid artery) prevented completion of the intended operation.

Follow-up studies were possible in only a few patients. Cases 7 and 8 were followed periodically in the clinic for ten and 17 years, during which time both patients continued to have seizures in spite of various anticonvulsant drugs given in apparently adequate amounts. Case 9 was followed for six years (until ten years of age), at which time she was still unable to speak, ate only strained food, and was not toilet trained. She displayed a mean temper at times and banged her head against the wall. This patient has since been institutionalized. When last seen in the clinic, proceedings were underway to institutionalize case 17.

DISCUSSION

This series of patients with agenesis of the corpus callosum differs in several ways from the cases reported in the literature and summarized by Carpenter and Druckemiller.[3] The incidence of hydrocephalus in this series (42 per cent) is considerably greater than that found in the literature (8.8 per cent). Marburg[15] has postulated that agenesis of the corpus callosum associated with hydrocephalus differs from the "genuine" callosal defect in that



FIGS. 8 and 9. *Case 10.* Lateral and anteroposterior projections of pneumoencephalogram demonstrating enormous dilatation of the ventricular system, widely separated lateral ventricles, and dorsal displacement of the third ventricle.

FIGS. 10 and 11. *Case 12.* Lateral and anteroposterior views of pneumoencephalograms showing widely separated, dilated lateral ventricle, angular dorsal margins of the lateral ventricles, elongated interventricular foramina, and tremendous dilatation and dorsal displacement of the third ventricle.

FIG. 12. *Case 18.* Posteroanterior projection of pneumoencephalogram revealing widely separated lateral ventricles, elongation of the interventricular foramina, and dilatation and dorsal extension of the third ventricle.

Fig. 13. *Case 18.* Anteroposterior view of pneumoencephalogram showing wide separation and dilatation of the lateral ventricles.

FIGS. 14 and 15. *Case 19.* Lateral and anteroposterior views of ventriculogram showing widely separated lateral ventricles, dilatation of the posterior horns of the lateral ventricles, angular dorsal margins of the lateral ventricles, and dilatation of the third ventricle with dorsal extension.

it develops in the second half of fetal life, while the "genuine" callosal defect develops in the first 14 days after conception. It is entirely possible that agenesis of the corpus callosum associated with hydrocephalus has a specific etiology and pathogenesis, although some degree of hydrocephalus (as seen in the dilated posterior horns of the lateral ventricles) is relatively common.

Focal and Jacksonian seizures in infants have a different significance than in adults, but the fact that 75 per cent of the seizures in these patients were

of this type is striking and may be due, at least in part, to the existence of the anomaly. The precise role of the interhemispheric commissural fiber systems in convulsive disorders have never been elucidated, but Van Wagenen and Herren[16] found that section of the corpus callosum in patients with generalized convulsions modified the seizure pattern. Following section of the corpus callosum seizures were usually unilateral and not associated with loss of consciousness. Hoefer and Pool[17] found that section of the corpus callosum in cats and monkeys raised the convulsive threshold and shortened the duration of seizures. Erickson[18] concluded that section of the corpus callosum in monkeys inhibited the spread of electrical stimuli from one hemisphere to the other. Kopeloff and his co-workers[19] reported that section of the corpus callosum in monkeys with experimentally-produced epilepsy caused complete restriction of the seizures to the side opposite the epileptogenic focus. The resulting unilateral seizures were said to have been more severe and more easily elicited than in animals with intact corpus callosum. It seems possible that the high incidence of focal and Jacksonian seizures in these patients may be due to deficient neopallial commissural fiber systems.

The physical and neurologic findings in these cases varied greatly and did not appear to fit any easily recognized pattern. Little support appears to be furnished for the thesis of a syndrome of the corpus callosum as postulated by Cameron,[20] Alpers and Grant,[21] Trescher and Ford,[22] and Sweet.[23] A synthesis of the various elements of this syndrome as suggested by these authors encompasses a wide variety of symptoms and signs, for example, apraxia, astereognosis, agraphia, forced grasping, disturbances of higher visual functions in the homonymous field of the nondominant hemisphere (pure visual alexia, object agnosia), marked mental disturbances (impaired memory, reasoning, and association of ideas), drowsiness, Korsakoff-like syndrome, and incontinence of urine and feces. Clinical study of patients in which the corpus callosum has been surgically sectioned partially and completely[16,24,25,26,27] does not confirm the existence of the syndrome hypothecated above, and experimental studies[28] in animals support the same conclusion. That is another example of the well-known difficulty and hazard of drawing conclusions concerning the relation of structure and function of the nervous system from patients suffering brain tumors and vascular insults.

The relationship, if any, between the corpus callosum and mental symptoms is difficult to determine. Mingazzini[29] expressed the opinion that mental symptoms were prominent with lesions of the corpus callosum, and Alpers[30] wrote on the mental syndrome of corpus callosum tumors, admitting that such neoplasms were not restricted to the latter structure. List, Holt, and Everett,[31] in a review of the clinicopathologic literature of lipomas of the corpus callosum, found mental symptoms common, but did not comment on any particular characteristics. Remitting mental symptoms are one of the striking features of Marchiafava's disease (primary degeneration of the corpus callosum), but the clinical picture is complicated by the presence of degeneration in the centrum ovale as well as by factors of arteriosclerosis and nutritional

deficiency. It would thus seem that in some way, as yet obscure, mental disturbances and intellectual deterioration are associated with most of the pathologic conditions involving the corpus callosum, including agenesis of that structure.

Although the diagnosis of agenesis of the corpus callosum during life should be suspected in infants and children exhibiting physical and mental retardation, focal or Jacksonian seizures, and/or hydrocephalus, it can rarely if ever be made on the basis of clinical findings alone. Plain roentgenograms of the skull do not reveal specific findings. Cerebral angiography failed to demonstrate evidence of this anomaly in cases reported by Mäurer,[32] Tarlov and Rosenberg,[33] and Carpenter and Druckemiller.[3] Sheldon and Peyman[4] found that cerebral angiography disclosed "wandering" of the anterior cerebral and pericallosal arteries which contrasted strikingly with the usual rounded and stretched appearance of these vessels. They suggested that angiography might be helpful in doubtful cases as well as in cases of lipoma of the corpus callosum. The diagnosis is readily made by encephalography and the characteristic features described by Davidoff and Dyke are considered pathognomonic. Surgical exploration has proved to be a poor diagnostic technic even in the hands of experienced surgeons and possesses no therapeutic value.

SUMMARY AND CONCLUSIONS

A study was made of 19 cases of agenesis of the corpus callosum, all but one of which were diagnosed during life. Two cases came to necropsy and confirmed the clinical (roentgen) diagnosis. Analysis of this material revealed the following:

1. Initial symptoms manifested by these 19 patients became apparent prior to three years of age in 89 per cent of cases.

2. Initial symptoms were focal or Jacksonian seizures in 37 per cent of cases, hydrocephalus in 31.5 per cent, and physical and mental retardation in 31.5 per cent.

3. Sixty-three per cent of the entire group had verified major seizures sometime during their illness. Such seizures were focal or Jacksonian in 75 per cent of cases.

4. Eighty per cent of the 15 patients studied by standard psychometric technics were found to be mentally retarded or defective.

5. Forty-two per cent of patients in this series were hydrocephalic.

6. It has been postulated that the high incidence of focal or Jacksonian seizures in patients with agenesis of the corpus callosum may be due to deficient neopallial commissural fiber systems which inhibit the spread of the seizure to the opposite hemisphere.

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Standardization of the Face-Hand Test

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A SIMPLE PERCEPTUAL TEST, the face-hand test, has been introduced in previous studies and the responses of normal subjects and of patients with psychiatric disorders described in detail.[1–6] The test consists of applying touch or pinprick stimuli simultaneously to the face and hand while the subject's eyes are closed. The subject is then asked to describe and to localize the percepts. Two general types of responses occur. The two stimuli may be perceived and localized correctly, or the subject may perceive only one stimulus and either not perceive the other (phenomenon of extinction) or mislocalize the second stimulus (phenomenon of displacement).[7] Most often the mislocalization or displacement occurs to another part of the subject's body, but occasionally there is displacement into extrapersonal space or onto the examiner (exosomesthesia).[8] Displacement of stimuli across the midline of the body (allesthesia) may also occur.[9]

Normal adults show errors in perception on the initial trials of the face-hand test. Characteristically these errors consist of extinction of the stimulus to the hand whereas the face stimulus is perceived correctly (phenomenon of face dominance). As tests are repeated the errors disappear so that by the tenth trial nearly all subjects correctly perceive both stimuli and then continue to be correct on subsequent trials. This type of response has been termed a "negative face-hand test." It occurs not only with normal adults but also in patients with schizophrenia, depression, or severe anxiety.

In contrast, patients with an organic mental syndrome show extinction and displacement after ten trials of testing or as long as testing is continued. Such a response is termed a "positive face-hand test." A "positive face-hand test" is also manifested by normal children, normal aged persons, and mental defectives.

Because of the differential response of these several groups of subjects, the face-hand test has become useful clinically in detecting the presence of organic brain disease. During the course of our studies, however, it has been noted that patients with an organic mental syndrome vary greatly in the type and

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frequency of perceptual errors. Also, subjects without organic brain disease occasionally manifest a positive face-hand test. The questions which arise from these observations are: 1) Is it possible to classify or standardize the different types of errors occurring in subjects with a positive face-hand test? 2) Is there a correlation between the types of responses and different groups of subjects? 3) Is there a type of response which can be said to occur only in patients with severe disease of the brain? The present study is an attempt to answer these questions.

METHOD AND RESULTS

Previous records of the face-hand test were reviewed for almost 1,000 patients with organic mental syndrome, normal adults, and schizophrenic adults, as well as lesser numbers of normal children, normal aged persons, and subjects with mental deficiency, depression, and severe anxiety. Additional groups of some of these subjects were also tested in a systematic manner with different types of stimuli. The criteria used to formulate a standardization of the face-hand test were: 1) type of perceptual error; 2) frequency of various errors with different stimuli (touch, rubbing or scratching, and pinprick); 3) effect on the frequency of errors when the subject observes the application of stimuli (factor of attention). Fifteen to 30 trials of the test were usually done for each subject.

TABLE 1
FEATURES OF POSITIVE FACE-HAND TESTS
(Persistent errors after 10th trial)

One-plus	*Two-plus*	*Three-plus*	*Four-plus*
Extinction only with touch stimuli.	Extinction with touch, rubbing, and pinprick stimuli. Occasional displacement with touch stimuli.	Extinction and displacement with touch, rubbing, and pinprick stimuli.	Same as three-plus with at least one of the following features: a) exosomesthesia, b) allesthesia, c) frequent perseveration, d) occurrence of errors while subject watches the stimuli being applied.

Based on these criteria, it was possible to divide patients showing a positive face-hand test into four groups. The characteristic responses for each group are summarized in table 1. These responses with examples are described more fully in the following paragraphs.

One-plus face-hand test: Subjects in this group show errors only of extinction and not of displacement. These errors occur only with touch stimuli. When pinprick is used, both stimuli are perceived correctly, although errors will again appear when touch stimuli are reintroduced.

Case 1.—A 64 year old man with mild diabetes was admitted with a history of difficulty in walking for the previous year and a half. For at least the same period of time he had been depressed, slept and ate poorly, and was impotent. The only neurologic finding was a slow, hesitant, shuffling gait. There was no evidence of peripheral vascular disease. The patient appeared depressed, showed psychomotor retardation, and cried readily. The sensorium was intact. Spinal fluid, electroencephalogram, and roentgenograms of

the spine were normal. The diagnosis was involutional psychosis, depressed type. The gait difficulties were thought to be secondary to the depression.

This patient showed a one-plus response on the face-hand test. A sample of his responses follows:

Stimulus	*Location*	*Response*	*Type of error*
touch	right cheek–left hand	right cheek	extinction
touch	left cheek–right hand	left cheek	extinction
touch	right cheek–right hand	right cheek	extinction
touch	left cheek–left hand	left cheek	extinction
touch	right cheek–left cheek	correct	
touch	right hand–left hand	correct	
touch	right cheek–left hand	right cheek	extinction
touch	left cheek–right hand	correct	
touch	left cheek–left hand	correct	
touch	right cheek–right hand	right cheek	extinction
touch	left cheek–left hand	left cheek	extinction
pinprick	right cheek–left hand	correct	
pinprick	left cheek–right hand	correct	
pinprick	right cheek–right hand	correct	
pinprick	left cheek–left hand	correct	
touch	right cheek–left hand	correct	
touch	left cheek–right hand	left cheek	extinction

Comment: Although this type of response occurs in patients with cerebral disease, it is not always characteristic for this group. It is also observed in patients with depression, as this case illustrates, and may occur in anxiety states, schizophrenia, and, occasionally, in normal adults.

Two-plus face-hand test: In this group extinction occurs with pinprick and rubbing stimuli as well as with touch stimuli. These errors may be just as frequent with both types of stimuli or may be more conspicuous with touch than with pinprick or rubbing. Displacement is not present, as a rule, but may occur on an occasional trial.

Case 2.—A 72 year old man had a five week history of mental and behavioral changes. These consisted of disorientation, confused behavior, and intermittent mutism. Examination showed an organic mental syndrome characterized by partial disorientation, defects in recent memory, evasions and circumlocutions in answering questions, denial of illness, and pain asymbolia. There were no other neurologic disabilities. The spinal fluid, electroencephalogram, and skull roentgenograms were normal. A pneumoencephalogram showed an increased amount of air over the cerebrum and increase in the size of the ventricles.

This patient's responses on the face-hand test characterize the two-plus type of response. A sample of these responses follows:

Stimulus	*Location*	*Response*	*Type of error*
touch	left cheek–right hand	left cheek	extinction
touch	right cheek–left hand	right cheek	extinction
touch	left cheek–left hand	left cheek	extinction
touch	right cheek–right hand	right cheek	extinction
touch	right cheek–left cheek	correct	
touch	right hand–left hand	correct	
touch	right cheek–left hand	right cheek	extinction
pinprick	left cheek–right hand	left cheek	extinction

Stimulus	*Location*	*Response*	*Type of error*
pinprick	right cheek–left hand	correct	
pinprick	left cheek–left hand	left cheek	extinction
pinprick	right cheek–right hand	right cheek	extinction
pinprick	left cheek–right hand	left cheek	extinction

Comment: This response occurs most often in patients with cerebral disease, although occasionally patients with anxiety states, depression, or schizophrenia may also exhibit it. It is not seen in normal adults.

Three-plus face-hand test: This group is characterized by the occurrence of displacement as well as extinction with both touch and pinprick stimuli. The frequency of extinction and displacement may be equal or unequal and, likewise, the number of errors with touch and pinprick will be variable.

Case 3.—A 57 year old chronic alcoholic was found in the street in a stuporous condition. His breath had an alcoholic odor and there was a laceration over his right forehead. There were no focal neurologic signs. During the first hospital day the patient gradually became fully conscious. Speech was rambling and at times almost incoherent. He was completely disoriented and had severe memory defects with confabulation. He expressed paranoid ideas and was hostile and assaultive. There were no hallucinations. Spinal fluid and skull roentgenograms were normal. The diagnosis was acute and chronic alcoholism with deterioration.

A sample of this patient's responses on the face-hand test, indicative of a three-plus response, follows:

Stimulus	*Location*	*Response*	*Type of error*
touch	right cheek–left hand	right cheek–left cheek	displacement
touch	left cheek–right hand	right hand–left hand	displacement
touch	right cheek–right hand	right cheek	extinction
touch	left cheek–left hand	correct	
touch	left cheek–right hand	left cheek	extinction
touch	right cheek–left hand	right cheek–left cheek	displacement
touch	right hand–left hand	correct	
pinprick	right cheek–left hand	right cheek–left cheek	displacement
pinprick	left cheek–right hand	left cheek–right cheek	displacement
pinprick	right cheek–right hand	right cheek	extinction
pinprick	left cheek–left hand	left cheek	extinction

Four-plus face-hand test: This group shows the most severe perceptual errors. In addition to frequent extinction and displacement, as seen in the three-plus group, one or all of the following phenomena may be seen with touch and pinprick stimuli: 1) exosomesthesia; 2) allesthesia; 3) frequent perseveration of responses; 4) occurrence of perceptual errors even while the subject keeps his eyes open and sees the areas stimulated.

Case 4.—A 60 year old man had a three year history of disorientation, forgetfulness, and loss of interest. On examination he showed a severe organic mental syndrome manifested by complete disorientation, marked memory defects, and inability to calculate. He was alert and cooperative. There were no other neurologic signs. Spinal fluid and skull roentgenograms were normal. The electroencephalogram showed moderate, diffuse, bisynchronous slowing with slow alpha. A pneumoencephalogram disclosed abnormal increased amounts of air in the subarachnoid spaces overlying the cerebral cortex.

A sample of the patient's responses, indicating a four-plus face-hand test, follows:

Stimulus	*Location*	*Response*	*Type of error*
touch	right cheek–left hand	right cheek	extinction
touch	left cheek–right hand	left cheek–extrapersonal space	exosomesthesia
touch	right cheek–right hand	right cheek	extinction
touch	left cheek–left hand	right cheek	perseveration
touch	right hand–left hand	correct	
touch	right cheek–left hand	right cheek–left cheek	displacement
touch	left cheek–right hand	left cheek–left hand	allesthesia
pinprick	right cheek–left hand	right cheek–left cheek	displacement
pinprick	left cheek–right hand	left cheek	extinction
pinprick	right cheek–right hand	right cheek	extinction
pinprick	left cheek–left hand	left cheek–extrapersonal space	exosomesthesia
pinprick (eyes open)	right cheek–left hand	right cheek–extrapersonal space	exosomesthesia

Comment: Three-plus and four-plus responses invariably indicate disease of the brain. They are never found in normal adults or in patients with psychogenic disorders.

These responses have been occasionally seen, however, in normal children under the age of six,[4] aged persons without manifest disease of the brain,[6] and mental defectives.[10] The distribution of responses of children and aged persons are related mainly to age. The youngest children and the oldest adults show three-plus and four-plus responses. With changes in age away from these extremes, one-plus and two-plus responses become more frequent. Of the subjects with mental deficiency, those with the lowest mental age have three-plus and four-plus responses, while one-plus and two-plus responses predominate in subjects with higher mental ages.

Table 2 summarizes the distribution of the four different types of responses among the various groups of subjects. Only patients with an organic mental syndrome show three-plus and four-plus responses. Such responses may be considered diagnostic of an organic mental syndrome.

DISCUSSION

In answer to the questions raised at the outset of this paper, our results indicate that four general types of positive face-hand tests occur and that

TABLE 2

PERCENTAGE FREQUENCY OF ONE-PLUS TO FOUR-PLUS POSITIVE FACE-HAND TEST IN DIFFERENT GROUPS OF SUBJECTS

	Negative F-H test	*One-plus*	*Two-plus*	*Three-plus*	*Four-plus*
Organic mental syndrome	10	7	25	33	25
Normal adults (below 60 years of age)	99	1	0	0	0
Schizophrenic adults	nearly all	occasional	rare	never	never
Patients with anxiety states	nearly all	occasional	rare	never	never
Patients with psychogenic depression (all age groups included)	70	22	8	0	0

these types can be correlated with different groups of subjects (table 2). Our attention was focused mainly on whether there was a type of response which occurred only in patients with severe disease of the brain. All adult subjects with a three-plus or four-plus response have organic brain disease. Such responses are never seen in normal subjects or patients with psychogenic disorders, even though these groups may occasionally show one-plus or two-plus responses.

Patients with cerebral disease manifesting a four-plus response invariably show the severest or most advanced form of mental changes. Otherwise there is no good correlation between the type of positive face-hand test and the severity of sensorial defects. Some patients with severe mental changes may have only a two-plus response. In addition, 10 per cent of patients with an organic mental syndrome have a negative face-hand test. It is realized that the use of a one to four-plus nomenclature for the groups implies an increasing degree of cerebral dysfunction. This nomenclature was used because of convenience and such an implication is not intended.

This classification of a positive face-hand test should be useful clinically. In testing neurologic patients, the exact type of positive face-hand test should be recorded, rather than the designation "the face-hand test was positive" as has been done until now. Such a procedure will make it easier to judge whether the type of positive face-hand test indicates definite cerebral disease or whether it may be a manifestation of anxiety or depression. The use of such a classification will also make it easier to compare the response of patients at different times during their illness. In addition, it is valuable in clinical experimental work, for it has been applied in studies of the effects of drugs on perception and the responses of patients to electroshock treatment. In such studies alteration in perception can be measured by observing the duration and incidence of the variety of positive face-hand tests during the periods of testing.

SUMMARY

A standardization of the face-hand test is presented. A positive face-hand test is designated as one in which errors persist after the tenth trial. Four classes of positive face-hand tests are recorded. A one-plus face-hand test consists of extinction only with touch stimuli. A two-plus response is characterized by extinction with pinprick and rubbing stimuli, as well as with touch stimuli. A three-plus response consists of extinction and displacement with touch, rubbing, and pinprick stimuli. A four-plus response has all the characteristics of a three-plus response and in addition at least one of the following features: a) exosomesthesia; b) allesthesia; c) perseveration of responses; d) occurrence of errors even while the subject observes application of the stimuli. Three-plus and four-plus responses invariably indicate disease of the brain in subjects over the age of six years. One-plus and two-plus responses occur in patients with brain disease but are also manifested by a small number of normal adults and patients with psychogenic disorders.

Patients with a four-plus response show the severest mental changes but the converse is not true. There is no correlation between the severity of the mental changes and the type of positive face-hand test manifested. Usefulness of this classification in the study of patients clinically and in experimental work is suggested.

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The tendency of the disease is to self-perpetuation; each attack facilitates the occurrence of another, by increasing the instability of the nerve elements. Hence the spontaneous cessation of the disease is an event too rare to be reasonably anticipated in any given case. Occasionally, however, convulsive attacks in infancy, which continue after all cause to which they could be attributed has passed away, cease spontaneously at four or five years of age; sometimes they do not afterwards recur, but too often they come on again at the period of the second dentition or at puberty. Attacks which have commenced before, and continued until puberty, rarely cease at that period. The expectation, firmly rooted in the popular mind, that attacks before the establishment of menstruation will cease when this has occurred is unjustified by facts. My own observations on this point agree perfectly with the statements of Herpin. It is extremely rare for menstruation to make any difference in such cases. After twenty years of age, spontaneous cessation does sometimes occur, and it becomes more frequent as life advances. It is, I believe, a more frequent event than writers on the disease have usually admitted, but is not sufficiently common to be reckoned on as an element in prognosis.

Marriage, as a rule, makes no difference to epileptics. The attacks occur afterwards with the same frequency and severity as before. In some patients they cease during pregnancy, but usually recur when the pregnancy is over.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Chronic Experimental Epilepsy in Macaca Mulatta

Lenore M. Kopeloff, Ph.D., Joseph G. Chusid, M.D. and Nicholas Kopeloff, Ph.D.

THE PRESENT REVIEW is concerned with experimental results obtained during the past 12 years in chronic epilepsy induced in Macaca mulatta.

MATERIALS AND METHOD

Aluminum compounds successfully used for the purpose of producing experimental epilepsy have included alums,* alumina, and alumina cream.[1] Our laboratory has routinely employed a precipitate (alumina cream) prepared according to the method described by Hawk and Bergeim[2] in which ammonium alum is treated at room temperature with dilute ammonium hydroxide. Such standard preparations of alumina cream have retained their epileptogenic properties for periods of at least two years. Commercial aluminum oxide powder washed with saline, autoclaved, and used as a moist sediment has also been used successfully, and commercially available gelatinous aluminum hydroxide has likewise proved highly effective.[3]

Linen or fiber disks used to apply the alumina cream were tooled to an inside diameter of 13 mm., a depth of 1.5 mm., and a capacity of approximately 0.2 to 0.25 ml.

RESULTS

Topical application of alumina cream to the cerebral sensorimotor cortex (figure 1) causes monkeys to become chronically epileptic.[1,4] Chronic Jacksonian epilepsy was produced with regularity in 50 of 51 monkeys treated

*Alums represent a class of compounds expressed by the general formula $M_2+ SO_4 \cdot M_2+++ (SO_4)_3 \cdot 24H_2O$; or $M+ M+++ (SO_4)_2 \cdot 12H_2O$, in which M+ is a univalent metal (alkali metals except lithium, ammonium, silver, or thallium) and M+++ is a trivalent metal (aluminum, iron, chromium). Alums need not contain aluminum (for example, potassium chrome alum); therefore, specific designation of particular alum compounds is desirable. When ammonia is added to an aluminum salt solution, a highly gelatinous precipitate of hydrous aluminum oxide is formed. The properties of such a precipitate depend upon the conditions of formation, age, and history of the particular sample.

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Presented before the American League Against Epilepsy, Boston, August 22, 1953.

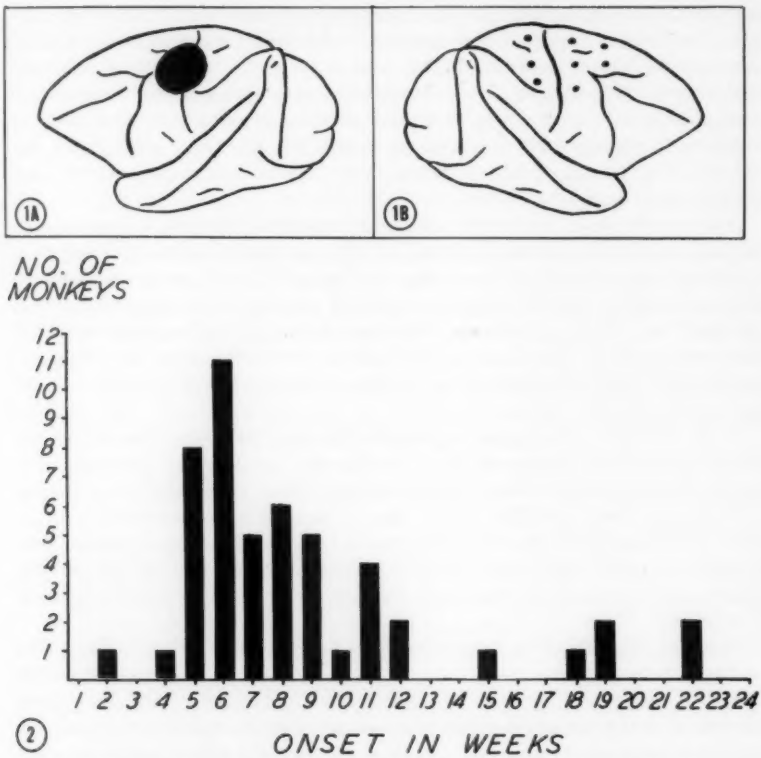

FIG. 1. Diagrams of lateral surface of cerebral hemisphere of Macaca mulatta showing *A*, common site of disk application (shaded area) and *B*, sites of multiple injection (dots).

FIG. 2. Graph showing time of onset of epilepsy in a group of 50 monkeys treated with alumina cream applied by disk to a cerebral sensorimotor area.

with alumina cream applied to one cerebral sensorimotor cortex and left in place. The time of onset of seizures in this group is indicated in figure 2. A seizure-free interval of several weeks followed treatment before clinically apparent motor convulsions were detected. In 43 of the 50 monkeys seizures commenced before the twelfth week, with a peak time of onset in the five to nine week period; in one instance they occurred as early as two weeks. Seizures in such animals usually began as a focal reaction in the contralateral limb or face, commonly progressing by Jacksonian spread to involve musculature of an entire side or of both sides. Variant motor phenomena such as tremor and myoclonus have also been noted.[5] On occasion the nature of the motor convulsive response could be related to the intensity of a precipitating or activating stimulation or stress, with myoclonus occurring at a lower inten-

sity while Jacksonian or generalized seizures followed more intense stimulation. Similarly it appeared that monkeys exhibiting visible tremors or myoclonus could be more readily thrown into major motor seizures by relatively mild stress or stimulation. The susceptibility of alumina-treated monkeys to precipitation of motor convulsions was evident after a stress stimulus of severe noisy prodding for a period up to one minute. Once established, the epileptic response generally persisted over a period of years (one verified instance of six and a half years).

The simultaneous application of a disk containing alumina cream to each cerebral sensorimotor cortex induced a highly intensified convulsive response. A violent state of epileptic reactivity also occurred in 14 monkeys in which disks containing alumina cream-precipitated proteins were applied to both principal sensorimotor cortices. However, when a second contralateral disk containing alumina cream was applied six to 18 months after an initial unilateral application, the intensity of motor convulsive manifestations was not appreciably altered.

Disks with alumina cream applied to the occipital, anterolateral frontal, lateral temporal, or anterior temporal cortex in a small group of animals did not produce clinically evident motor seizures. Prior application to a contralateral lateral temporal lobe cortex for six months (three monkeys) or to contralateral occipital lobe for three and a half months (two monkeys) did not appear to influence significantly the epileptic response resulting from subsequent application of a disk with alumina cream to the cerebral sensorimotor cortex.

Subtotal ablation of the precentral motor area of one or both sides of the cerebrum, followed later by the application of an alumina cream disk to the surface of the ablated zone or to the adjacent motor cortex, did not inhibit subsequent development of motor seizures or electroencephalographic abnormalities in nine of 11 monkeys.[6] In the two monkeys which failed to react, the removal of tissue was greatest, extending almost to the surface of the lateral ventricle at several points.

Application of alumina cream to the intact precentral motor cortex with simultaneous subtotal ablation of the contralateral precentral motor cortex in three monkeys induced a greater degree of convulsive reactivity than in a control series of seven monkeys without ablation treated similarly with alumina cream.[7] Application of alumina cream to the intact precentral motor cortex in four monkeys which had been treated nine to 18 months previously with alumina cream at the site of ablation of the contralateral precentral motor area resulted in status epilepticus. Three of these animals died within one week after the onset of status. Existence in the precentral motor area of the monkey of "inhibitory" fibers whose interruption at the cortical or callosal level facilitates convulsive reactivity was suggested.

Section of the corpus callosum after onset of seizures in four monkeys and prior to onset of seizures in three monkeys caused complete restriction of subsequent seizures to the contralateral side.[8] Resulting unilateral attacks,

however, were considerably more severe and more easily induced than those observed in a large control series of epileptic monkeys with intact corpus callosum. Section of the corpus callosum after bilateral seizures had been established caused focal motor status epilepticus on the side opposite the focus in three of four monkeys, while section of the corpus callosum prior to application of alumina cream to one sensorimotor cortex resulted in easily elicited seizures but not status epilepticus. Section of the corpus callosum greatly reduced but did not completely inhibit the spread of abnormal electrical discharges to the cerebral hemisphere opposite the focus.

Intracerebral injection of alumina cream has also been effective in producing chronic epilepsy in the monkey. A single injection of 0.1 ml. into a cerebral sensorimotor cortical area produced epilepsy in one of two animals.[4] *Multiple intracerebral injections* into eight standard areas (figure 1) of the principal sensorimotor cortex induced an intense epileptic syndrome with early onset of epileptic manifestations.[9–12] In the initial phases of the convulsive response, constant twitching muscular contractions and jerks of varying amplitude occurred, with a predisposition to Jacksonian or generalized seizures upon stress, agitation, movement, or excitement. These animals were considered to be suffering the simian counterpart of human partial constant epilepsy. After a period of several weeks the twitching movements became less pronounced, but the monkeys continued to exhibit spontaneous Jacksonian seizures and marked susceptibility to major seizures upon prodding or stress. Shallow, rather minute, multiple cortical needle scarification of a 1 mm. square surface of the precentral motor cortex through a thin layer of alumina cream (0.1 ml.) did not produce clinical epilepsy in three monkeys during 13 to 17 months of observation.

Subcortical injection of 0.1 to 0.2 ml. of alumina cream induced convulsive seizures in four monkeys when the preparation was placed in the following positions: medial nuclear groups of thalamus bilaterally, putamen bilaterally, region of subcallosal fasciculus, and white matter adjacent to cingulate sulcus.[13] In six monkeys no motor seizures occurred with lesions of the lateral nuclear group of thalamus unilaterally or bilaterally, hypothalamus, tegmentum of pons and decussation of brachium conjunctivum, and caudate nucleus with opposite putamen. In these animals electroencephalographic abnormalities, although uniformly present, were more pronounced in the epileptic group, especially when seizures were evident. In a monkey in which alumina cream produced a small lesion centered on a centromedian thalamic nucleus, apparently painful bilateral paresthesias developed which persisted through 14 weeks of observation; they were improved after bilateral excision of parietal cortex.[14]

CONVULSIVE THRESHOLD

The convulsive threshold to rapid intravenous injection of 10 per cent pentamethylenetetrazole (Metrazol) was significantly lower (2.8 to 6.3 mg./kg.) in 70 per cent of a group of 16 epileptic monkeys than in a control group of

seven untreated monkeys (8.5 to 29 mg./kg.).[15,16] Intramuscular injections of 8 to 28 mg./kg. produced motor convulsions, usually focal in onset, in all 17 epileptic monkeys while none of the seven control animals convulsed with dosages up to 44 mg./kg. Only two of the latter exhibited convulsions with 48 mg./kg., the highest dosage tested. The convulsive response of 16 epileptic monkeys to a standard test dose of 16 mg./kg. of Metrazol was similar, whether administered subcutaneously or intramuscularly. It was therefore concluded that differentiation between epileptic and non-epileptic monkeys could be made more readily on the basis of their convulsive reaction to Metrazol injected intramuscularly than by the rapid intravenous route. In epileptic monkeys the motor convulsive thresholds to intravenous or intramuscular Metrazol did not always parallel susceptibility to seizures elicited by prodding or stress.

The convulsive response (time of onset, character, intensity, and frequency of convulsive seizures) induced by topical application of alumina cream to the cerebral sensorimotor cortex was not significantly altered in eight monkeys after intensive intramuscular treatment with the anticholinesterase, di-isopropyl fluorophosphate (D.F.P.), for periods up to 17 weeks.[17] Electroencephalographic changes that could be attributed to D.F.P. occurred in the later phases of treatment, particularly when evidence of D.F.P. intoxication was pronounced, and consisted mainly of mild to moderate diffuse slowing of dominant rhythms in the record.

HISTOPATHOLOGIC STUDIES

Histopathologic studies of the brain of monkeys made epileptic following the application of disks containing alumina cream to the cerebral sensorimotor cortex revealed changes indicative of a chronic progressive meningocortical cicatrix.[1,4,18,19] However, a similar type of lesion was produced by disks containing control preparations which failed to induce convulsive seizures at any time during a long observation period. It was felt, therefore, that the pathologic changes observed were insufficient by themselves to account for the convulsive manifestations. Lesions in the monkey cortex following treatment with disks containing alumina cream resembled some scars associated with seizures in man and were characterized by a meningocortical scar with underlying increased cortical vascularity, gliosis, pathologic neurons, and subcortical degeneration. Following multiple intracerebral injections of alumina cream, a meningocerebral cicatrix was present extending over the zone of cerebral injections with scarring of underlying cortex and white matter (figure 3).[9,12] Usually injection sites and needle tracks were grossly visible in coronal brain sections. Microscopic examination revealed that needle tracks contained a more or less homogeneous injection mass with collections of gitter cells most prominent near the borders (figures 4 and 5). A variable degree of brain tissue reaction occurred around the borders of the needle tracks. Vascular zones containing many vessels with thickened endothelial layers extended from the edges of injection sites. Adjacent cerebral tissue showed evidence of severe neuronal changes, intense astrocytic gliosis, markedly increased vascularity, and demyelinization.

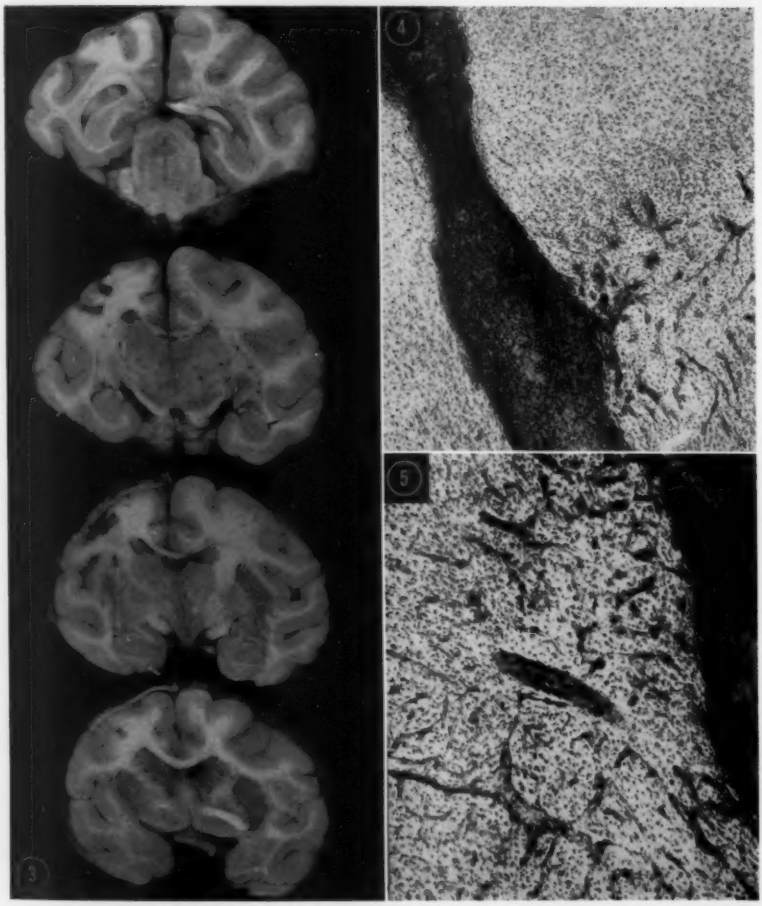

FIG. 3. Coronal sections through brain of a monkey sacrificed 11 months after multiple injections into right cerebral hemisphere.

FIG. 4. Needle track with adjacent cerebral tissue of a monkey five weeks after multiple intracerebral injection treatment. Hematoxylin and eosin stain.

FIG. 5. Reactive vascular zone bordering injection mass two months after multiple intracerebral injection treatment. Hematoxylin and eosin stain.

Locally the cortical scar produced by application of alumina cream to the cortex was different chemically from the rest of the cortex as shown by the random fluctuation of its noble metal potential but not its pH.[19] Sometimes the scar area exhibited electrical seizures of the general form seen in the cortex during grand mal seizures. These disturbances, it was believed, could

spread through the cortex to contiguous areas or provoke similar disturbances in remote regions of the cortex and some deeper structures, but only in those to which the discharging region sent axons or collaterals. Change in the pH and noble metal potential in a given region were the same and bore the same relationship to the electrical discharge in it during the spontaneous seizure of the chronically convulsant cortex as during similar induced seizures.

ELECTROENCEPHALOGRAPHIC PATTERNS

The electroencephalograms of monkeys made epileptic following application of alumina cream to the sensorimotor cortex were characterized by focal changes, chiefly delta activity, random spikes, and sharp activity, appearing first prior to the onset of major seizures.[20–22] A secondary or "mirror" focus of electroencephalographic abnormality frequently developed in the opposite cerebral sensorimotor area. Maximal electroencephalographic disturbance was usually associated with generalized convulsions; minimal changes persisted in some cases after cessation of seizures. Intramuscular or intravenous subconvulsive doses of Metrazol have been valuable in activating abnormal or pathologic sites, with accentuation or precipitation of abnormal patterns.[9,21–23]

Representative illustrations of electroencephalographic patterns of monkeys after alumina cream treatment have been published.[8,20–22] Principal associated findings included irregular delta activity, high-voltage spike potentials, numerous sharp formations, and fast activity. Occasional bursts of serial slow waves, spike and dome discharges, and spike and dome variants were noted in the region of application of a disk with alumina cream, with subsequent spread to other areas of the brain. Although representative patterns could be selected to illustrate specific features, many records were apt to include mixtures of abnormal types. Illustrated types have included the following: 1) unilateral focus (slow wave, slow wave and spike); 2) bilateral abnormality (predominance of focus, marked spread to opposite side); 3) spike and dome discharges; 4) Metrazol activation effects on: marked unilateral abnormality, mild focus with minimal spread, and marked bilateral abnormality.

Following multiple intracerebral injections of alumina cream into a cerebral principal sensorimotor cortical area, there appeared in the early epileptic phase more or less continuous high amplitude spike or spike and slow wave discharges, most intense over the injection sites (figures 6 and 7).[9,12] When relatively small muscle segments or groups were involved in the twitching or myoclonic responses, a direct correlation between components of the electroencephalogram and visible abnormal muscle motor activity could not be established; occasionally, however, spike discharges in the electroencephalogram seemed to occur synchronously with visible abnormal motor activity for short intervals, especially when massive focal myoclonic responses occurred. Spike activity in subsequent stages was generally less prominent, being replaced by high amplitude serial slow wave activity. In a monkey with very shallow intracortical multiple injections of alumina cream, an un-

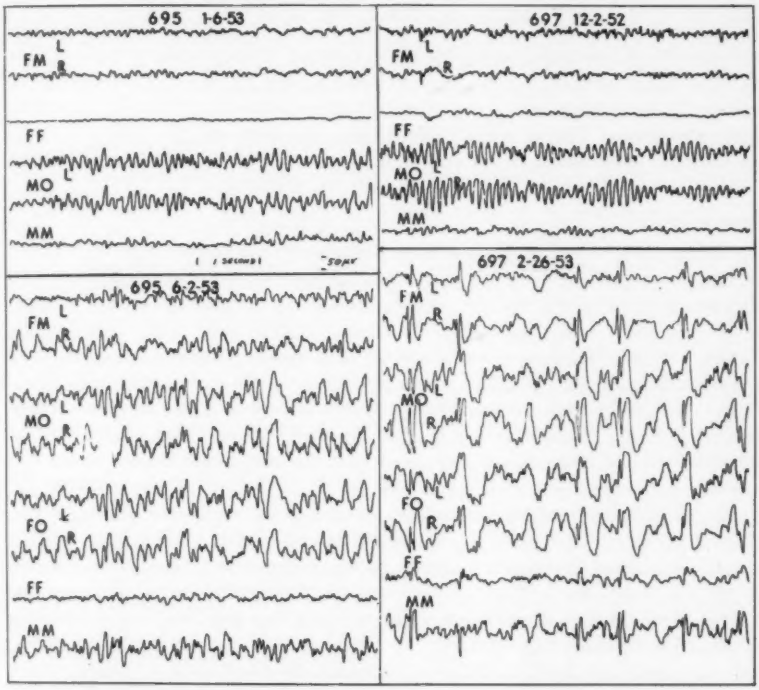

FIG. 6. Electroencephalograms of monkeys after treatment with autoclaved commercial aluminum hydroxide (gelatinous). At left, record 24 weeks after application of disk to right sensorimotor cortex; at right, record five weeks after multiple intracerebral injections into right cerebral sensorimotor cortical area. (Reproduced with permission of *Electroencephalography and Clinical Neurophysiology.*)

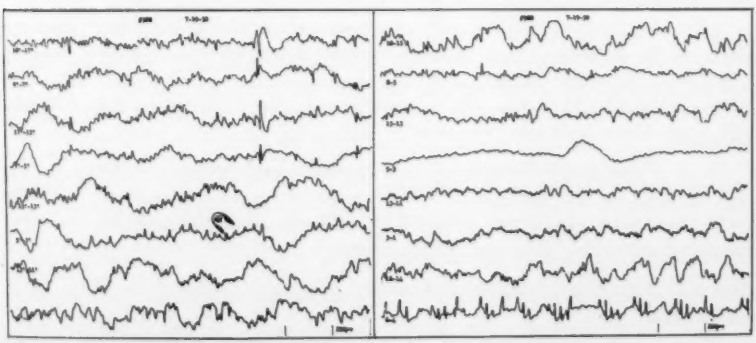

FIG. 7. Electrocorticogram (Nembutal anesthesia) of scarred area five months following multiple intracerebral injections of alumina cream.

usual pattern was observed consisting of spindle bursts of 18 to 22 per second superimposed upon very slow wave background activity. Apparent transmission of electroencephalographic abnormalities (spikes, spike and slow wave, or slow wave activity), especially to homologous areas of the contralateral cerebral hemisphere, was a prominent feature particularly during the earlier epileptic phases. The activating effect upon the electroencephalogram of relatively small doses of Metrazol (0.1 to 0.15 ml. of 10 per cent solution) administered by rapid intravenous injection was again noted.

DISCUSSION

Others have also found aluminum compounds effective in the production of chronic experimental epilepsy. Thus, Pope and his co-workers[24] applied alumina cream by disk to the cerebral cortex and reported chronic epilepsy in the monkey with associated electroencephalographic and histochemical findings. Cure, Rasmussen, and Jasper,[25] in presenting their findings in seven monkeys treated with alumina cream applied by means of a linen disk to the motor cortical surface, stressed the activation effects of Metrazol administered in small doses. Walker and Johnson[26] applied "alum protein cups" to the frontal cortex of 20 monkeys and noted that the cortex in the area of the cup became very excitable, with wandering of the self-propagating response following electrical stimulation from area to area of the cortex for unusually prolonged periods. Cure and Rasmussen[27] described the clinical and electroencephalographic findings in a group of eight monkeys treated with alumina cream applied to the cerebral motor cortex or the insular cortex. Johnson and Walker[28] stated that 12 monkeys with epileptic foci produced by application of alum-precipitated egg white to the cerebral cortex showed a lower Metrazol convulsive threshold than normal animals. Gastaut and his collaborators[29] have described epilepsy in the cat resulting from the injection of alumina cream into the amygdaloid nucleus. Sloan, Ransohoff, and Pool,[30] following injection of alumina cream into the amygdaloid regions of monkeys, reported the production of seizures characterized by sudden onset of altered state of consciousness, mastication, and persisting altered consciousness.

Alumina cream treatment may also cause alteration of function when applied locally at lower levels of the neuraxis. Kennard[31] has injected alumina cream into the spinal subarachnoid space and into the spinal cord of cats, producing abnormal causalgia-like sensory states characterized by hyperalgesia.

SUMMARY

Some of the major features and characteristics of epilepsy induced in Macaca mulatta in this laboratory by the application of alumina cream to the brain have been presented. Clinical, pathologic, neurophysiologic, and electroencephalographic findings are discussed.

Fiber disks made from Synthan, grade L, natural, ⅝ inch rod, Synthan Corp., Oaks, Pa.

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CLINICAL PATHOLOGIC CONFERENCE

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Section Editor

Presented by D. P. Jones, M.D. and Margaret C. Swanton, M.D.

REPORT OF CASE

A 42 year old woman was admitted to Watts Hospital, Durham, North Carolina on January 12, 1953, in coma. Twenty-four years previously she had spent nine months in another hospital because of continuous headaches and a sudden attack of blindness lasting two days. Thereafter she remained apparently well except for intermittent headaches until January 1952, when she experienced a fainting sensation but did not lose consciousness nor convulse. Six months later she had another "dizzy" attack and fell down beside her bed, but recovered rapidly and did not sustain any injury.

One and one-half hours before hospital admission she was found unconscious on the floor. On examination she was cold and cyanotic, and breathed slowly and deeply. The temperature was 102° F., pulse rapid and uncountable, and blood pressure 80/? mm. Hg. There was evidence of acute pulmonary edema on auscultation, and blood-stained frothy sputum was present about the mouth.

The optic disks were normal, the pupils small and fixed, and the eyes divergent. There was slight drooping of the right side of the mouth, and the tendon jerks were increased in the right arm and leg. There was no neck rigidity and the limbs were flaccid, more so on the left side. During examination spasms of rigidity of the trunk, neck, and limbs developed intermittently.

On the next day respiration was normal, but tachycardia persisted and the temperature reached 105° F. There remained a divergent squint with fixed pupils, but the left pupil was now larger than the right. There was some stiffness of the neck and both plantar responses were extensor. The patient died six days after admission with hyperpyrexia of 107° F., but no further change in neurologic signs was observed.

Laboratory findings: An atraumatic lumbar puncture on the day after admission showed fluid at an initial pressure of 300 mm. of water. The fluid was reddish in color and contained 1400 red blood cells per cu. mm. The cerebrospinal fluid protein was 48 mg. per cent. Other findings were as follows: blood sugar: 251 mg. per cent on admission, 147 per cent two days later; blood urea: 22 mg. per cent; blood Kahn test: negative; urine: traces of albumin and of sugar on occasions; roentgenogram of skull: marked excavation of the pituitary fossa but no erosion of the clinoid processes (figure 1).

DISCUSSION

DR. JONES: The history emphasizes two acute illnesses over a period of 24 years, during which intermittent headache was the main symptom. The first episode consisted of blindness lasting two days, a symptom consistent with localization to the prepituitary region and suggesting, in the light of subsequent events, either a transient pressure disturbance or possibly extravasation of blood into the optic nerve sheaths.

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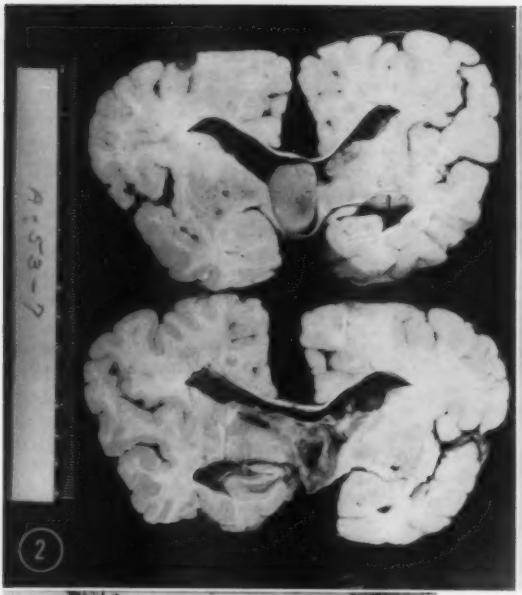
FIG. 1. Roentgenogram of skull showing marked excavation of the pituitary fossa.

In the terminal illness there was involvement of the hypothalamus and of the midbrain. The history of coma, flaccidity with tonic spasms, elevated cerebrospinal fluid pressure, and bilateral third nerve involvement suggests a midbrain lesion arising as a result of a tentorial pressure cone. The pupillary constriction may be evidence of a lesion in the periaqueductal region of the midbrain also, or it may have been hypothalamic in origin. The other signs, including vasomotor collapse, pulmonary edema, hyperpyrexia, and transient glycosuria, are all compatible with a hypothalamic lesion, and the radiologic demonstration of sellar enlargement is strong evidence in support of this localization. Lastly, there is the presence of subarachnoid blood which may have entered the space directly as from an aneurysm, or may have been primarily intraventricular.

It is clear that all these signs were of recent development. There is evidence also from the nonprogressive history and the absence of papilledema that the intracranial pressure was probably normal until the terminal illness. Therefore, one must postulate a chronic lesion causing enlargement of the sella turcica and yet failing entirely to give rise to signs of raised intracranial pressure, to compression of the visual pathways or nerves running in the cavernous sinus, or to signs of intrinsic pituitary disease.

It is unlikely that the sellar enlargement was due to dilatation of the third ventricle, since an obstructive lesion would almost certainly have led to papilledema and a more progressive symptomatology in the course of 24 years. An intrasellar pituitary tumor is also unlikely in that the early episode of blindness could not have been caused by any process confined to the pituitary fossa, and it is improbable that extension beyond the diaphragm occurred at that early date. The terminal episode moreover does not suggest rupture of a pituitary lesion beyond the confines of the sella. The symptoms then are those of visual field defects caused by pressure on the nearby optic chiasm or tracts, and there is rarely any immediate gross increase of intracranial pressure.

The most probable explanation is a parasellar lesion of slow growth, deforming the sella and displacing nerves in the cavernous sinus without compressing them. Of such lesions a suprasellar cyst can be excluded, since it occurs earlier in life and, if of this duration, would probably have shown signs of calcification in its wall. A meningioma into which hemorrhage occurred is possible, but it is rare for a meningioma on the base of the skull not to interfere with cranial nerves near it. The most likely explanation is a congenital aneurysm of the carotid artery, occurring in either the cavernous or the supraclinoid portion of the vessel. Such aneurysms may reach considerable size without causing oculomotor palsies and may be discovered accidentally by the presence of calcification in them. In this case one would postu-



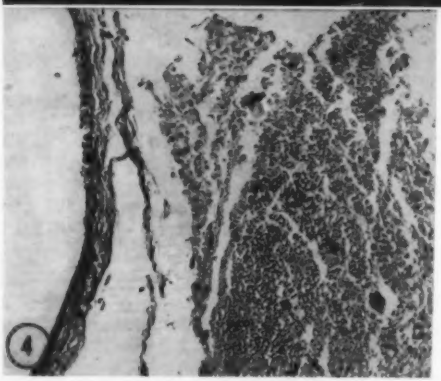


FIG. 2. Coronal sections of cerebrum with dilated ventricles. Upper section shows hyaline cyst contents within the distended third ventricle. Lower section through posterior wall of cyst shows left thalamic hemorrhage. (Branching dark bands on right side are engorged veins.)

FIG. 3. Wall of third ventricular cyst, in a segment where cells retain columnar shape.

FIG. 4. Cyst wall and lateral wall of third ventricle with encephalomalacia. Wedge shaped cellular area adjacent to cyst wall consists chiefly of "gitter cells."

late terminal rupture of an aneurysm with bleeding into the hypothalamus, intracerebral hematoma formation, and a terminal acute hydrocephalus caused by herniation of the brain into the tentorial opening.

PATHOLOGIC DISCUSSION

DR. SWANTON: Autopsy on this moderately obese 42 year old female revealed no major pathologic findings outside of the cranial cavity. The lungs showed hypostatic congestion and a mild lobular pneumonia. Chronic thyroiditis of the Hashimoto's struma lymphomatosa type was present in small areas of the gland. No anatomic evidence of hypertension

was found in the cardiovascular system. The urinary system showed no abnormalities.

On examination of the cranial cavity after removal of the brain, the sella turcica was enlarged, measuring 2.5 cm. in diameter and 1.5 cm. in depth. The floor was paper thin and the posterior clinoid processes appeared eroded. The compressed pituitary gland, remaining intact in the bottom of the fossa, was only 3 mm. in maximum thickness. Despite this, it showed no histologic evidence of pressure atrophy of the parenchyma. A recent thrombus partially occluded the left lateral dural venous sinus. The carotid arteries and circle of Willis and its branches showed no abnormality. The leptomeninges were thin and transparent, and the cerebrospinal fluid was clear. The cerebral hemispheres were symmetrical, but gyri were moderately flattened and sulci proportionately narrowed. There was, however, no evidence of herniation through the incisura of the tentorium cerebelli or into the foramen magnum. On the ventral aspect of the brain stem, the floor of the third ventricle was seen to be markedly depressed, widened, and less than 0.5 mm. thick, apparently stretched tautly over a firm, smooth intraventricular mass. The optic chiasm and optic tracts were broader and flatter than normal, and the latter showed histologic evidence of peripheral pressure atrophy and demyelinization. Had this patient been examined before becoming unconscious, a visual field defect would almost certainly have been included in the clinical findings.

In coronal sections of the formalin-fixed brain the lateral ventricles showed pronounced symmetrical dilation, with thinning out and stretching of the corpus callosum and septum pellucidum and rupture of the latter. The distended third ventricle was entirely filled by a firm, white, smooth-surfaced, oval mass of cartilagenous consistency measuring 2.2 cm. dorsoventrally, 1.5 cm. from side to side, and 2 cm. anteroposteriorly (figure 2). The hyaline, milky, translucent center of this mass was covered by a thin, shiny, white membrane. The only area of attachment of the latter to nervous tissue was at the anterior end of the roof of the third ventricle. Elsewhere the mass could be lifted out to reveal smooth ependyma lining a greatly dilated third ventricle with compressed walls. The mass impinged upon the dilated foramina of Munro and the aqueduct. Histologically the membrane consisted of a thin layer of fibrous tissue lined by a single layer of flat to low columnar cells, some of which were ciliated (figure 3). The contents of this cyst wall was a hyaline coagulum with a few shadowy remnants of cells. Some sections of the compressed ventricular wall showed a rim of encephalomalacia, and all showed demyelinization of adjacent tissue (figure 4). The gross and microscopic findings are typical of a colloid cyst of the third ventricle.

This mass had produced other distant effects in addition to and more important than the internal hydrocephalus. The anterior half of the left thalamus had a subependymal area of brownish softening less than 10 mm. in maximum diameter (figure 2). Histologically this showed relatively recent necrosis and hemorrhages, with a wide surrounding zone of edema and neuronal necrosis without stromal necrosis. This had been present long enough to have elicited microglial cell reaction, although few "gitter cells" had developed. Erythrocytes were fairly well preserved but erythrophagocytosis was pronounced, especially around vessels. A few neutrophils were present. It is not unreasonable to postulate that this hemorrhage adjacent to the ventricle was the source of the red blood cells found in the spinal fluid five days before death.

Continuous with this were subependy-

mal hemorrhages and foci of necrosis in the medial portion of the posterior thalamus, 18 x 7 mm. in maximal cross sectional dimensions, ventral to which there were small satellite hemorrhages. Hemorrhagic necrosis did not extend as deep as the internal capsule, but edema and neuronal degeneration and necrosis were present throughout the thalamus. It is conceivable that there was functional damage to the internal capsule without clear morphologic change. Recent hemorrhage was also present around the pineal body and, along with early necrosis, in the superior colliculi and periaqueductal gray matter in the upper mesencephalon. Oculomotor nuclei showed no loss of tissue continuity, but many neurones in both lateral portions showed necrosis with complete karylolysis. These mesensephalic lesions explain the neurologic findings related to pupillary reflexes and extraocular muscles.

This distribution of hemorrhagic necrosis is consistent with compression of venous drainage from these structures en route to the internal cerebral veins, as a result of distortion of the size and shape of the third ventricle. The presence of hyalinized thrombi in an occasional small vein and partially occluding a larger vein in a section through the upper mesencephalon suggests retarded flow in these vessels prior to sufficient compression along their course to result in severe tissue damage. The clinical manifestations of the patient's terminal episode can be accounted for by the hemorrhagic necrosis and adjacent areas of edema and neuronal damage.

The final diagnosis of the central nervous system lesion in this 42 year old woman was colloid cyst of the third ventricle. Secondary to this were internal hydrocephalus involving the lateral ventricles, pressure atrophy and necrosis of the wall of the third ventricle, partial demyelinization of the optic tracts, and recent hemorrhage and necrosis of the left thalamus and upper mesencephalon.

The automatic action is often regarded as constituting the epileptic seizure, and the attacks presenting this feature have, following Esquirol, been called "masked epilepsy," or "epilepsia larvata" after Morel. Whether this mental automatism may replace and represent an epileptic seizure, or whether it is always a post-epileptic phenomenon, is a question still undecided, which will be presently considered.

It is certain, however, that the automatic state often succeeds an attack, and is then essentially a post-epileptic phenomenon. According to an hypothesis suggested by Anstie and Thompson-Dickson, and applied by Hughlings Jackson, it is the result of the exhaustion of the highest cerebral centres by the discharge, and the consequent temporary loss of the control which these should exercise over complex centres just below them, which consequently act in an insubordinate and automatic manner.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

CASE REPORT

Sensorimotor Induction Syndrome in Unilateral Disequilibrium

Lipman Halpern, M.D. and David Perry Kidron, M.B., Ch.B.

THE SYNDROME of sensorimotor induction, based on the earlier experiences of Goldstein,[1–3] von Weizsaecker,[4–6] and Quadfasel[7] and more recent systemic investigations,[8–12] is a well defined clinical entity. It is not as rare as might appear and would be recognized much more frequently were more attention given to its characteristic symptomatology. The following observations represent a further contribution to the clinical manifestations of this syndrome.

CASE REPORT

A married woman, aged 45, with two healthy children, worked as a dietitian in a medical clinic up to two years ago. When the patient was 24 years old, she had experienced attacks of dizziness, a feeling of fullness in the ears, blurring of vision, and general weakness. A heaviness was felt on the left side of the body which was more pronounced during the attacks. These disturbances recurred repeatedly during the succeeding years, and were so bad at times that she was confined to bed for weeks. She was kept under observation in the outpatient department for a long time, but the increasing number and severity of her attacks necessitated hospitalization twice in the last year.

On admission the only abnormal finding on general clinical and laboratory examinations was an eosinophilia, which was familial and which varied from 20 to 40 per cent. Neurologic examination did not reveal any abnormalities in the cranial nerves. The pupils were equal, central, and circular, and reacted to light and accommodation though the latter was not well sustained. The eyes moved freely in all directions and there was no nystagmus. Ophthalmologic examination showed visual acuity of 5/6 in both eyes and normal visual fields and fundi. During the attacks of dizziness it was noted that the left eye closed and remained so until the dizziness passed. Otologic examination revealed normal hearing and normal vestibular function on both sides. The tone and voluntary movements of the limbs were normal and equal on the two sides, but there was noticeable weakness of the left arm and leg on objective testing. In addition the left arm showed an occasional tremor both at rest and in movement, and slight adiadochokinesis. Superficial and deep sensibility in all its qualities, including stereognosis, was normal. The limb reflexes were exaggerated generally, possibly more in the left leg. The abdominal reflexes were absent, and no Babinski, Chaddock, Oppenheim, or Rossolimo signs were found. In addition there existed disturbances of equilibrium and of the sensory functions, which will be described later.

The electroencephalogram and roentgenogram of the skull were normal. Lumbar puncture showed a clear fluid at normal pressure and the Queckenstedt test was negative. Chemical analysis of the fluid showed glucose 79 mg. per cent, chlorides

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710 mg. per cent, protein 25 mg. per cent, with the Nonne and Pandy tests negative. The fluid culture was sterile and no cells were present. The Wassermann and Kahn reactions in the cerebrospinal fluid and in the blood were negative.

SPECIAL EXAMINATION OF INDUCTIVE SENSORIMOTOR MANIFESTATIONS

Disturbances of Equilibrium

With eyes open the patient kept her head straight; however, as soon as the eyes were closed, the head turned spontaneously but slightly to the right, without her being aware of it. This occurred whether sitting or standing, and at the same time the patient's body inclined backwards and to the left. When her head was inclined passively to the extreme left she felt unwell, but when it was turned passively to the right she felt well and comfortable.

When the patient was asked to stretch out her arms in front of her and to keep them in this position with her eyes shut, the right arm stayed at the same level. The left arm fell with "nystagmoid" movements to a level of 30 or 40 cm. below the starting point without the patient being aware of it, and at the same time deviated outward about 10 to 15 cm. Repeated examination showed the same findings, the degree of deviation changing only slightly. When the patient's head was turned passively to the right, displacement of the left arm occurred more slowly and to a lesser extent; when her head was turned to the left the deviation of the arm was accelerated and increased. These findings were confirmed on repeated examination.

When the patient was asked to raise her legs and to keep them at a certain level, with her eyes closed, the left leg deviated downward and outward without the patient being aware of it. When she was asked to raise one leg and then place the other leg at the same level, with her eyes shut, the left leg was always placed lower than the right one.

As mentioned above, the patient's body inclined spontaneously backwards and to the left, and this was more pronounced when her eyes were closed. Further it became evident that standing, too, was influenced by the passive changing of the position of the patient's head. While standing and with the head turned to the right she felt more at ease, and the tendency to fall backwards and to the left was less evident than when her head was kept straight. While standing, and with her head turned passively to the left, she felt more uncertain of herself and the tendency to fall became distinctly increased.

Examination of the patient's gait with her eyes closed revealed a deviation to the left when walking forward or backward. When the patient was asked to walk back and forth several times a zigzag pattern of walking resulted.

Disturbance of Visual Perception

The patient stated that from time to time objects appeared blurred, especially when looking to the left. When reading she often missed letters and the lines often appeared to be tilted; thus, when reading Hebrew from right to left the beginning of the line seemed to be at a higher level than its end. Frequently the pictures on the wall seemed to be hanging obliquely, so she "straightened" them, only to notice after a few days that the pictures were actually not hanging straight; she realized that she had been mistaken in her previous impression and corrected their position once more.

When the patient was asked to look at a right angle chalked on a blackboard, she saw it correctly when using both eyes or her right eye alone. When using the left eye only, she saw the vertical component deviated to the left at its upper end to an angle of 8 degrees, and at the same time the horizontal component was raised at its right end to about 6 degrees, so that the whole right angle appeared

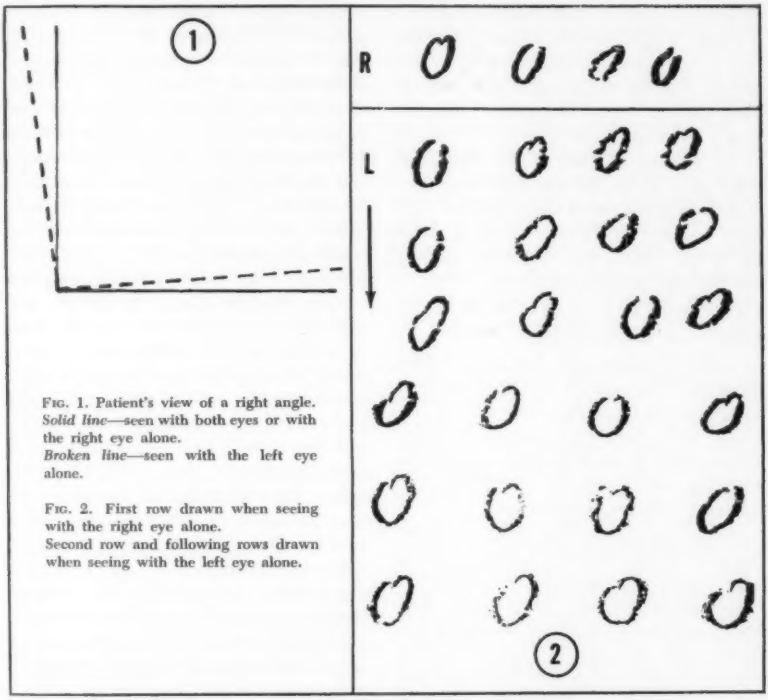

FIG. 1. Patient's view of a right angle.
Solid line—seen with both eyes or with the right eye alone.
Broken line—seen with the left eye alone.

FIG. 2. First row drawn when seeing with the right eye alone.
Second row and following rows drawn when seeing with the left eye alone.

tilted to the left (figure 1).

When shown an unshaded cube drawn in perspective, she did not differentiate among the separate lines when using her left eye only, but saw the picture as a whole and tilted to the left. This visual deviation was not influenced by a change of the position of the head or of the arms.

The patient was asked to draw a row of circles with the left eye closed, and then to draw another row below that of equal size with the right eye closed. The latter circles appeared slightly larger than those drawn when using the right eye only. She was asked to continue drawing circles in the same manner using the left eye only, with the result that every row of circles was drawn larger than the preceding one (figure 2). Similar results were obtained when drawing other figures such as triangles.

When the patient was shown a vertical line interrupted by small interspaces she saw it correctly when using both eyes or when using the right eye alone. When using the left eye only, the line appeared continuous in its upper and central parts.

When shown a series of various colors she differentiated normally among them when using both eyes or only the right eye. When using the left eye only, the same series of colors – dark tints at the blue end of the spectrum – appeared darker, and the longer she looked at them the darker they became. This applied particularly to the colors at the left end of the row, which were dark blue,

green, and purple. She was then shown a range of lightly-tinted colors at the red end of the spectrum, but even with prolonged looking these colors did not appear darker, except for two at the extreme left end of the row.

To determine whether the change of color perception on the left was associated with the colors themselves or with their position, colors were reversed. Tested in this way, colors at the left end of the row again appeared darker.

Disturbances of Perception in the Haptic and Tactile Spheres

While standing with her eyes closed, the patient was asked to hold a rod vertically in front of her; she held it inclined with the upper end to the left. When asked to hold the rod horizontally with her eyes closed, she held it with the left end inclined downwards.

When the patient was asked to close her eyes and identical wooden blocks were placed in each hand, she described the block in her left hand as thicker. She continued to hold the blocks in her hands and said after a further interval that the block in her left hand was not only thicker but also longer than that in her right hand. It thus became apparent that the longer the test was continued the more evident was the difference in perception. When the same test was repeated with the patient's head turned passively to the right, she stated that the block in her left hand was still larger and longer than that in her right hand. When her head was turned to the left, she felt that the block in her left hand was much thicker and longer than formerly.

DISCUSSION

The symptoms described above are typical of the syndrome of sensorimotor induction. As far as is known at present, this syndrome in its entirety is composed of the following symptoms: 1) motor disturbances resulting in a unilateral postural deviation of the whole body and its extremities; 2) monocular or even binocular impairment of the visual perception of spatial coordinates and of geometrical figures; 3) monocular micropsia or macropsia; 4) monocular or even binocular dissolution of color perception; 5) change in the size of written script and displacement of the line of writing; 6) disturbed discrimination of spatially close optic stimuli; 7) deviation in the tactile and haptic perception of the vertical and the horizontal; 8) unilateral acoustic deviation from the midline outward of a sound transmitted to both ears; 9) change in the tactile perception of size of objects, resulting in unilateral microstereognosis or macrostereognosis; 10) unilateral faulty estimation of weights and distances; 11) unilateral disturbed discrimination of closely spaced tactile stimuli; 12) unilateral diminution of the sense of vibration; 13) extensive mutual influence of motor and sensory functions.

The abundance of symptoms seemingly unrelated at first glance can be traced back to a common basic disturbance. In spite of variations the syndrome shows certain basic common features in various patients.

A unilateral disequilibrium affecting the left side of the body was a prominent feature in this patient. It manifested itself as an unconscious deviation outward and downward of the extremities on the left, as a tendency to fall to the left when standing, and as a deviation to the left whether walking forward or backward. To render the physiopathologic mechanism taking place here more understandable, one must keep in mind that normal statokinetic stability is guaranteed by a steady perception of the horizontal ground plane and of the vertical planes passing symmetrically through the two halves of the body. In a unilateral disturbance of the equilibrium, which also appeared in this patient, the statokinetic perception is changed in such a way that the subjective midline of the

body and the subjective horizontal plane are displaced on one side. The main characteristic of the syndrome of sensorimotor induction consists of the fact that this displacement of the statokinetic system of the body causes inductively a deviation in the sensory perception of the vertical and horizontal coordinates in the visual, haptic, and sometimes also in the tactile and acoustic spheres. This deviation in sensory perception manifests itself characteristically on that side of the body which corresponds with the side of disequilibrium. As was shown above, this patient suffering from left-sided disequilibrium, also had an induced left-sided sensory deviation in the haptic and visual spheres. Thus when asked to place a rod vertically or to look with the left eye only at a vertical line she displaced the rod and the line outward to the left and a horizontal line downward to the left.

On the basis of a thorough clinical analysis, it was demonstrated that the syndrome of sensorimotor induction is composed of primary and secondary symptoms. To the primary symptoms belong the phenomena of unilateral deviation, which manifest themselves systematically in the motor and sensory spheres on the same side of the body, the motor disturbances constituting the preliminary condition of the syndrome. These phenomena are the basic symptoms, because by their equal inductive effect they represent the characteristic features of the syndrome and are in fact its constant components, in contrast to its inconstant secondary symptoms which affect solely the functions of sensory perception. It was demonstrated that the disorganization of statokinetic stability, which manifests itself in the primary symptoms of sensorimotor deviation, under certain circumstances can effect a de-differentiation of the sensory perception as to quality and altered projection as to quantity. It must be kept in mind that these altered manifestations of sensory function, in spite of normal sensory organs, represent therefore "secondary disturbances of perception"[13] and are the inconstant secondary components of the syndrome. To these sensory phenomena belong the symptoms of impaired discrimination of visual and tactile stimuli, of weight differences, and of fine vibration stimuli resulting from a qualitative de-differentiation of perception. Further we have to include the symptoms of quantitative changes of perception which manifest themselves as micropsia or macropsia, microstereognosis or macrostereognosis.

The qualitative de-differentiation of visual perception showed itself in this patient as a partially disturbed discrimination of fine optic stimuli and as a partially changed color perception. When looking with her left eye only, she perceived a dotted line in its upper and middle parts as a continuous one and saw dark colors becoming gradually darker, with those situated at the extreme left of the field of vision seeming darkest. Light colors, especially different shades of red, were perceived normally even on continuous looking with the left eye only, with the exception that colors at the extreme left of the field of vision appeared darker too. This confirmed former findings that, in contrast to the early disappearance of red caused by an anatomic lesion of the optic nerve, this color and its shades were steadily preserved in the present patient and in those described by the author earlier. In addition there existed in this patient a further difference in the visual perception between the outer and inner sectors of the left field of vision. This became apparent when the sequence of colors, which appeared to be darker, was inverted, as well as when a vertical dotted line was perceived as a continuous one in its upper and middle parts. The fusion of these parts of the line only can be explained thus, that on subjective deviation of its upper

part to the left it fell in the extreme outer sector of the left field of vision, while its lower part was perceived outside this zone.

This finding of an unequal qualitative de-differentiation in the same eye, made for the first time in this case, is of special interest. The greatest inequality showed itself in the extreme left outer field of vision which is situated functionally nearest to the effect of motor deviation. Quantitative changes in visual perception consisted in this patient of macropsia of the left eye, which gradually became more evident as a given pattern was copied repeatedly. A similar change of perception in the tactile sphere manifested itself as macrostereognosis of the left hand. These disturbances, which affected both organs of sensory perception of externals, showed themselves on the side of the disequilibrium and were influenced inductively in the same sense.

An important symptom of the syndrome consists further of the mutual influence of motor and sensory functions. The influence of head posture on these functions is of chief importance and is encountered most frequently.[14] As will be remembered, this patient kept her head straight when her eyes were open. However, when the eyes were shut, her head turned spontaneously and unconsciously to the right. Tests also showed that passive turning of the head to the left was not only unpleasant subjectively but also increased objectively the speed and extent of the descent of the left arm. In addition, in the sensory sphere, the left-sided stereognostic overestimation of size was increased too. When the patient's head was turned to the right, this position was not only pleasant to her but effected also a correction of the existing disturbances. The extent of descent of the left arm was diminished and the tendency to fall spontaneously to the left was visibly lessened. Turning of the head to the right, occurring spontaneously when visual control was excluded, is therefore a biologic regulating factor and represents a corrective symptom. Spontaneous closing of the left eye which occurred at the climax of the disease, without the patient being able to explain it, must be mentioned in this connection. It must be kept in mind that the monocular visual deviation in the perception of coordinates of space is sometimes aggravated to such a degree in these patients that in binocular vision, "optic coordinates' vertigo,"[15] results. This occurred in the present patient also at the climax of the disease, and the left eye closed spontaneously to exclude the disturbance which was caused by it, in analogy to the same procedure in diplopia. As can be seen, this symptom represents a protective mechanism to exclude an annoying stimulus. Both the closing of the left eye and the turning of the head to the right are therefore significant mechanisms of protection against stimuli from the outside and biologic regulation from within. This renders the organism more efficient under the prevailing pathologic conditions.

Another phenomenon of interest is the latent period which can be observed clearly in the development of sensory disturbances. This became apparent in the visual sphere when the patient was asked to copy figures and to look at colors. The longer she continued, the more these disturbances were aggravated. The same findings were obtained in the tactile sphere with regard to estimation of size. The longer an object was kept in the left hand, the more the macrostereognosis was increased. From this point of view, too, these findings confirm the validity of our basic conception that the secondary disturbances of sensory perception represent induced disturbances. As in every physiologic function, the factor of time is significant for their development and dynamics.

In view of the fact that unilateral sys-

tematic disequilibrium is decisive and obligatory for the production of the primary symptoms and for the whole syndrome, a supervestibular localization for this syndrome was assumed to be in the cerebellum and in the frontal lobe. The difference consists chiefly in the side of the manifestation. With cerebellar lesions the syndrome manifests itself homolaterally, and with frontal lesions contralaterally. In our patient the anatomic localization of the syndrome should be assumed to be in the left cerebellum, possibly on the basis of a monosymptomatic disseminated sclerosis, because of the appearance of the disease at an early age and the remissions of long duration. The assumption of a cerebellar localization is further supported by the varying reduction of power in the left arm and leg, which certainly gave the impression of a cerebellar hemiparesis. Apart from this cerebellar hemiparesis which, in the opinion of such clinicians as Ferrier, Luciani, Horsley, Bianchi, and Mann,[16] must be attributed to cerebellar asthenia, the tremor of the left arm, appearing at times at the height of the disease, was also considered to be of cerebellar origin.

With regard to localization of the syndrome, the cerebellum seems to play the chief role. In connection with this, the recent electroanatomic investigations of Snider[17] and his co-workers are of special interest since they reveal visual, tactile, and auditory areas within the cerebellum. As a result of these investigations, he stated that the cerebellum acts both in motor and sensory spheres, and that these sensory spheres do not subserve any known conscious function. On the basis of these findings, Snider demands a new and broader conception of cerebellar function and even states that workers in this field have been entirely too lethargic about recognizing this sensory action. Snider's findings obtained by electroanatomic means correspond very well with our clinical investigations on primary sensorimotor symptoms of deviation which manifest themselves in the motor, visual, tactile, haptic, and acoustic spheres, unknown to the individual. Further, if one keeps in mind the recently confirmed fact of the corticopontocerebellar connections, among others, with the contralateral frontal brain, and the recent findings that the above mentioned cerebellar sensory areas are connected with the same cerebral areas in reciprocal projection, then the same anatomic considerations should be applied as well to the frontal localization of this syndrome. These new electroanatomic findings can, therefore, make an additional contribution to the anatomic foundation of the syndrome of sensorimotor induction.

SUMMARY

The typical picture of the syndrome of sensorimotor induction was found in a patient suffering from left-sided unilateral disequilibrium, probably due to disseminated sclerosis. Apart from the already known symptoms of this syndrome, an unequal de-differentiation of the visual function in the left eye and a distinct latent period in the dynamics of the secondary disturbances of sensory perception were observed. The symptomatology and localization of the syndrome were determined, while taking into consideration its physiopathologic mechanisms and the finding of cerebellar sensory areas and their reciprocal corticopontocerebellar projections. The syndrome of sensorimotor induction represents a clinical entity which occurs more frequently than is generally supposed.

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In fits which begin locally, the spasm is not always clonic in the commencement; it may be at first tonic and afterwards clonic, as in a typical attack, and this although the fits are very limited in range. In one patient, for instance, the attacks were limited to the right arm and right side of the face, and commenced by tonic flexion of the fingers, first at the metacarpophalangeal joints, and then at the other joints, the flexion being greatest toward the ulnar side. The thumb was inverted or pressed against the first finger. Next the elbow-joint was gradually flexed, and the arm adducted by the pectoralis, so that the hand was brought in front of the chest. After an arm had got into this position, the tonic gradually passed into clonic spasm exactly as in an ordinary epileptic fit. This patient had also some attacks which began in the face, and a few which began in the right leg. There was a probability (although not conclusive evidence) that he was the subject of cerebral tumor, but his seizures are here mentioned because they are particularly instructive as an illustration of the characters of this form of seizure. Different parts, as the face and arm, being affected in succession, often presented, at the same moment, different stages of convulsion. For instance, when the face was affected first, and the arm secondarily, there was frequently clonic spasm (second stage) in the face, and tonic spasm (first stage) in the arm. In slight attacks involving face and arm, the leg often escaped altogether, but in severe attacks it was involved in the tonic and clonic spasm. In less severe seizures the leg was the seat of tonic spasm only, although the face and arm presented both forms of spasm. In some of these attacks a change in the form of tonic spasm in the leg was observed to occur at the time of the change from tonic to clonic spasm in the arm. The leg was always rigidly extended, and at first the foot was inverted and the great toe pointed downwards and inwards. When, however, the change in the form of spasm occurred in the arm, the foot ceased to be extended and inverted, the ankle-joint became flexed and the great toe over-extended so as to point upwards.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

NEWSLETTER

MARCH, 1954

Howard D. Fabing, President
Walter O. Klingman, President-Elect
Francis M. Forster, Vice-President
Alexander T. Ross, Secretary
Dave B. Ruskin, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

Program Committee Organizes Scientific Sessions

On January 16 and 17, the AAN program committee made final selections of papers for presentation at the scientific sessions of the annual meeting of the American Academy of Neurology to be held at the Shoreham Hotel, Washington, D. C. (April 26 to May 1)....According to program chairman Francis M. Forster, dean and professor of neurology at Georgetown University, "The scientific program is indeed outstanding and provides much new information in both experimental and clinical fields. The task of selecting was a most difficult one; so many papers were submitted by an unusually large number of distinguished investigators and clinicians."

Program Highlights Therapy and Research

An important feature of the scientific sessions (April 29-May 1) is a symposium on "gap areas" and innovations in the treatment of some common neurologic disorders, including poliomyelitis, meningitis, paraplegia, barbiturate intoxication, myasthenia gravis, cerebral palsy, headache, and neuralgia. Also to be presented are several papers concerned with new departures in experimental neurology and a series of reports on unusual clinical entities. Among the subjects treated are experimental cerebral palsy (Clinton N. Woolsey), the pathophysiology of pain (E. A. Spiegel); brain metabolism in epilepsy (Donald B. Tower); investigations of the primate amygdala (Maitland Baldwin). Added to these papers are the interesting epidemiologic investigations on the high incidence of amyotrophic lateral sclerosis in the Western Pacific (Leonard T. Kurland) and a follow-up study of Western equine encephalitis in California (Knox Finley), as well as presentation of the changing front of research in poliomyelitis by Henry W. Kumm of the National Foundation for Infantile Paralysis....All available space has been taken for an interesting array of scientific exhibits, which are supplemented by exhibits from voluntary health organizations interested in the neurologic field and technical exhibits....A complete printed program of the coming meeting will be mailed to all members well in advance.

Joint Session With Epilepsy League The AAN scientific program will terminate in a joint session with the American League Against Epilepsy on Saturday, May 1, at which a report of the legislative committee of the League on state and federal laws affecting epileptics will be made by Roscoe Barrow, dean of the College of Law, University of Cincinnati....The meeting of the American League Against Epilepsy will continue through Saturday and Sunday (May 1 and 2).

Special Courses to Precede Scientific Sessions In its efforts to be of service to members and others interested in the field of neurology, the AAN will offer, for the fourth consecutive year, seven special review courses as part of the annual meeting in Washington. These courses, which will be held April 26-28, are to be on the hypothalamus, (A. L. Sahs, chairman); neuropathology (Fae Tichy, chairman); diseases of the spinal cord (B. Boshes, chairman); neurophysiology (J. L. O'Leary, chairman); coma (J. R. Brown, chairman); reflexes (R. N. DeJong, chairman); and headache (A. P. Friedman, chairman). Part of the course in neurophysiology will be given at the new Clinical Center of the National Institutes of Health, Bethesda, Md. Enrollment in the courses is by advance application, which should be directed to Dr. A. B. Baker, 19 Millard Hall, University of Minnesota, Minneapolis 14, Minn.

Walter H. Judd To Be Guest Speaker The Honorable Walter H. Judd, distinguished Congressman, physician, and outstanding authority on the Orient, will be the AAN guest speaker at the joint luncheon of the Academy and its Woman's Auxiliary, Thursday, April 29. Dr. Judd, whose forceful speeches at the last Republican national convention will be long remembered, has had a rich and varied career. Born in Rising City, Nebraska, he obtained his M.D. from the University of Nebraska and later became a surgeon at the Mayo Clinic. The next step in his career was to be a medical missionary in China where he also became versed in the philosophy and politics of the Orient. From 1934 to 1938 he lectured throughout the United States on American foreign policy in the Pacific, advocating a boycott of Japanese goods and an embargo on shipments of war materials to Japan. Later (1938-40), he returned to the practice of surgery in Minnesota, and in 1941 was elected to the 78th Congress, in which capacity he has served ever since. Dr. Judd will speak on China.

Social Activities The Academy tradition of providing an informal but glowing program of social activities will be continued in the Washington meeting. The annual Academy cocktail party and banquet will be held on Friday, April 30 (no prepared speeches), followed by dancing in the Shoreham's famous Terrace Room. Invited as honor guests to the banquet are the Surgeon

Generals of the Army, Navy, Air Force, and Public Health Service, the Medical Director of the Veterans Administration, and the Director of the National Institutes of Health....Arrangements have been made for tours to many points of interest in the nation's capital....The activities of the Woman's Auxiliary begin with an "early bird" party on the afternoon of April 28, to which all members are invited. Entertainment will be provided by the Georgetown Chimes, a celebrated choral group of ten from Georgetown University. Also planned for the ladies, in addition to the joint luncheon, is a special luncheon and fashion show in the Palladian Room, Friday, April 30.

* * * * * *

International Neurologic Reunion To Convene in Paris

The Nineteenth International Neurologic Reunion, organized by the French Neurological Society (Societe Francaise de Neurologie), will be held in Paris June 1-2. The day following the International Reunion the French Neurological Society will hold its usual monthly meeting. A symposium on the neurologic sequelae of treated tuberculous meningitis is the central problem to be discussed at the International Reunion. All members and associate members of the French Neurological Society are invited to attend and participate in the program. All neurologists, who are not members of the French Society but wish to participate in the program of the International Reunion, should apply before the first of May to the Secretary-General, Dr. Jean Sigwald, 68, boulevard de Courcelles, Paris (XVII°).

Memorial Volume For Dr. Globus

The Journal of Neuropathology and Experimental Neurology has dedicated a volume (XIII, No. 1, Jan. 1954) to Dr. J. H. Globus (1885-1952), one of the founders and for eleven years the executive editor of the journal. The memorial volume contains a dedication by Israel Strauss and a biographic sketch by Arthur Weil which traces Dr. Globus's career from his birth in White Russia to his final achievements as a distinguished teacher, neuropathologist, and clinician in New York. Interesting insight into the character and philosophy of Dr. Globus is given as "An Unwritten Editorial" by his son, Rudo S. Globus. The remainder of the volume consists of many articles by noted authorities in neuropathology and clinical neurology.

$1000 in Prizes For Dissertations on Epilepsy

The American League Against Epilepsy announces the Jerry Price Memorial Prizes (contributed jointly by Mr. and Mrs. Fred Markham and the League) for original essays on any aspect of epileysy. The contest is open to students of any approved medical school in the United States or Canada. The first prize is $500, the second prize $200, and third prize $100.

In addition, there are book prizes for other contestants and possible publication of one or more essays in the journal, EPILEPSIA. Essays should be original, typed double-spaced, and preferably not more than 5000 words in length. Contestants should mail their essays before August 1, 1954, to Dr. J. K. Merlis, Secretary, American League Against Epilepsy, 150 South Huntington Avenue, Boston 30, Mass.

* * * * * *

American Board Results At the annual examination of the American Board of Psychiatry and Neurology, held in New York City (Dec. 14-15), 17 candidates were certified in neurology. The successful candidates are: William Amols, New York City; Abraham S. Effron, Paterson, N. J.; Paul S. Jarrett, Miami, Fla.; Howard Paul Krieger, Hewlett, N. Y.; Harold Allen Ladwig, Omaha, Neb.; Stanley Lesse, New York City; Leslie Gerard Lloyd, Long Beach, Calif.; Richard Milton Paddison, Haddonfield, N. J.; Alvin L. Robins, Bethesda, Md. (supplementary certification); Bertram Edward Sprofkin, Nashville, Tenn.; Charles Van Buskirk, Minneapolis, Minn.; Maurice Victor, Boston, Mass.; Charles Wesley Watson, West Newton, Mass.; George J. Wright, Jr. (supplementary certification); Eugene L. Youngue, Jr., Pittsburgh, Pa. (supplementary certification). Psychiatry and neurology: Harold Dillon, Philadelphia, Pa., and John Rensselaer Whittier, Englewood, N. J....At the meeting of the board, Kenneth Appel of Philadelphia was elected president; David A. Boyd, Jr., continues as secretary-treasurer....The date for the spring 1954 examination is May 10-11.

Briefs Horace W. Magoun is the 1953 winner of the Cerebral Palsy-Max Weinstein award, a plaque and $1000, for his studies of factors promoting regeneration of nerve fibers and of the physiology of the cerebral cortex in basal ganglia in relation to cerebral palsy....Peter G. Denker has been appointed professor of neurology and director of the department of neurology and psychiatry at the New York Polyclinic Hospital and Medical School....Jan Cammermeyer has joined William Windle's section on neuroanatomy in the National Institute of Neurological Diseases and Blindness....The Myasthenia Gravis Foundation announces the award of a grant of $1500 to Robert S. Schwab to assist in research at the Myasthenia Gravis Clinic at Massachusetts General Hospital....Dr. Frank Brown Berry has succeeded Dr. Melvin A. Casberg as Assistant Secretary of Defense for health and medical affairs....The Western Society of Electroencephalography will hold its eleventh annual meeting March 7 and 8 at the Del Monte Lodge, Pebble Beach, California.

Percy Bailey

PROGRAM OF THE
AMERICAN ACADEMY OF NEUROLOGY
Sixth Annual Meeting
April 26 – May 1, 1954

Shoreham Hotel *Washington, D.C.*

Review Courses in Basic and Clinical Neurology

April 26, 27, 28, 1954

Intensive review courses in basic and clinical neurology will be given preceding the annual meeting, sponsored and arranged by the American Academy of Neurology.

Courses will be held as follows:

The Hypothalamic Region—April 26, 1954

Neuropathology—April 26, 1954

Coma—April 27, 1954

Diseases of the Spinal Cord—April 27, 1954

Neurophysiology—April 27-28, 1954

The Reflexes—April 28, 1954

Headache—April 28, 1954

Additional information regarding these review courses may be obtained by writing to Dr. A. B. Baker, 19 Millard Hall, University of Minnesota, Minneapolis 14, Minnesota.

THURSDAY, APRIL 29, 1954

Morning Session 9:00 a.m.

Chairman: Robert B. Aird, *San Francisco, California.*

Secretary: Thomas Auth, *Washington, D.C.*

Studies in Experimental Cerebral Palsy: Bilateral Sensorimotor and Total Decortications

Clinton N. Woolsey and Ann M. Travis, *Madison, Wisconsin*

Clinical and Electrographic Studies of Hemispherectomized Patients

Richard Zarling, David R. Johnson, and Lyle A. French, *Minneapolis, Minnesota*

Myelomalacia and Multiple Cavitations of the Spinal Cord Secondary to Adhesive Arachnoiditis: An Experimental Study

Orville T. Bailey, *Indianapolis, Indiana* and Robert L. McLaurin, *Cincinnati, Ohio*

The Pathophysiology of Thalamic Pain

E. A. Spiegel, H. T. Wycis, M. Kletzkin, and E. G. Szekely, *Philadelphia, Pennsylvania*

An Investigation of the Primate Amygdala

Maitland Baldwin, *Bethesda, Maryland*

Business Session 11:30 a.m.
Howard D. Fabing, presiding

THURSDAY, APRIL 29, 1954

Afternoon Session 2:00 p.m.

Chairman: Francis M. Forster, *Washington, D.C.*

Secretary: G. Bushnell Smith, *Washington, D.C.*

Symposium on Therapy in Neurology

Poliomyelitis: Treatment Review

A. B. Baker, *Minneapolis, Minnesota*

The Treatment of Meningitis

A. L. Sahs, *Iowa City, Iowa*

The Treatment of Barbiturate Intoxication

Fae Tichy, *Minneapolis, Minnesota*

The Present Therapy of Paraplegia

Benjamin Boshes, Eli L. Tigay, and Israel Zivin, *Chicago, Illinois*

The Treatment of Headaches and Neuralgias

Francis L. McNaughton, *Montreal, Canada*

Prostigmine-Induced Muscle Weakness in Patients With Myasthenia Gravis

L. P. Rowland, I. A. Jaffe, L. Berg, M. C. Korengold, and G. M. Shy, *Bethesda, Maryland*

FRIDAY, APRIL 30, 1954

Morning Session 9:00 a.m.

Chairman: Thomas W. Farmer, *Chapel Hill, North Carolina*

Secretary: David P. Jones, *Chapel Hill, North Carolina*

Epidemiologic Investigations of Amyotrophic Lateral Sclerosis, with Special Reference to the Mariana and Caroline Islands of the Western Pacific

Leonard T. Kurland, *Bethesda, Maryland* and Donald W. Mulder, *Rochester, Minnesota*

Trends in the Status of Neurology

Lothar B. Kalinowsky and H. Houston Merritt, *New York City*

The Afferent Projections of the Vagus and the Superior Laryngeal Nerves in the Brain Stem and the Cerebellum

Robert L. Lam, *St. Louis, Missouri*

Complications of Cerebral Angiography

Alberto D. Kaplan and A. Earl Walker, *Baltimore, Maryland*

A Year and a Half Follow Up Report on the 1952 Western Equine and St. Louis Encephalitis Epidemic in the Central Valley of California

Knox H. Finley, *San Francisco, California*

Business Session 11:30 a.m.
Howard D. Fabing, presiding

FRIDAY, APRIL 30, 1954

Afternoon Session 2:00 p.m.

Chairman: A. L. Sahs, *Iowa City, Iowa*

Secretary: R. A. Utterback, *Iowa City, Iowa*

The Changing of Front of Research on Poliomyelitis

Henry W. Kumm, National Foundation for Infantile Paralysis, *New York City*

REPORTS OF UNUSUAL CLINICAL ENTITIES

Postpartum Pituitary Insufficiency

Thomas Farmer and Charles E. Flowers, Jr., *Chapel Hill, North Carolina*

Puerperal Hemiplegia
Harold Stevens, *Washington, D.C.*

Spontaneous Subluxation of the Atlanto-axial Joint in Rheumatoid Spondylitis (Marie-Strumpell Disease)

Murray E. Margulies, *Brooklyn, New York*

Cerebral Involvement in Generalized Cytomegalic Inclusion Disease in the Newborn, with Advanced Periventricular Calcification and the Presence of Rosenthal Fibers

Webb Haymaker, *Washington, D.C.* and George H. Fetterman, *Pittsburgh, Pennsylvania*

Progressive Cerebral Cortical Degeneration (Alpers' Disease)

R. A. Utterback, *Iowa City, Iowa*

Pulseless Disease: Central Nervous System Manifestations

Russell N. DeJong, Giles Bole, and Robert D. Currier, *Ann Arbor, Michigan*

The Nature and Extent of the Biochemical Lesion in Epileptogenic Cerebral Cortex. An Approach to its Control *in vitro* and *in vivo*

Donald B. Tower, *Bethesda, Maryland*

SATURDAY, MAY 1, 1954

Morning Session 9:00 a.m.

JOINT SESSION

American Academy of Neurology
and
American League Against Epilepsy

Chairman: Pearce Bailey, *Washington, D.C.*, President, American League Against Epilepsy

Secretary of the American League Against Epilepsy, Jerome K. Merlis, *Boston, Massachusetts*

Chairman of the Program Committee, American League Against Epilepsy, Milton K. Shy, *Bethesda, Maryland*

The Relationship Between EEG Changes and Eye Centering on Brain Stem Stimulation

Daniel S. Feldman, Leroy A. Sugarman, Paul Teng, Robert Werman, and Philip S. Bergman, *New York City*

The Clinical Differential Diagnosis of the Brief Loss of Consciousness

Hal C. Gregg and Augustus S. Rose, *Los Angeles, California*

Diamox—A Carbonic Anhydrase Inhibitor: Its Use in Epilepsy

Sidney Merlis, *Islip, New York*

Report of Legislative Committee of the American League Against Epilepsy

Rocsoe Barrow, Dean, College of Law, University of Cincinnati

Howard D. Fabing, Chairman, Legislative Committee, American League Against Epilepsy

Open Discussion of Report of Legislative Committee

Adjournment, American Academy of Neurology, 11:30 a.m.

READ BY TITLE

Electrodiagnosis in Poliomyelitis

Alex J. Arieff and Norman Dobin, *Chicago, Illinois*

The Effects of Fungus Infections of the Nervous System Following Cortisone Therapy

Louis Boshes, Albert Milzer, and Helen Maclean, *Chicago, Illinois*

Spinal Epidural Tumor in Hodgkin's Disease

J. G. Chusid, C. G. de Gutierrez-Mahoney, and A. Rottino, *New York City*

Evaluation of Post-Concussive Subjective Complaints

Peter G. Denker and Gerald Perry, *New York City*

A Clinical Study of Two Thousand Cases of Migraine and Tension Headaches

Arnold P. Friedman, Theodore J. C. von Storch, and H. Houston Merritt, *New York City*

Mixed Tumors of the Parotid Gland with Brain Metastasis

Sidney Gross and Arnold P. Friedman, *New York City*

Encephalomyelitis Accompanying Rubella Treated with Gamma Globulin

Frederick H. Hesser, Thomas M. Drislane, and Robert W. Graves, *Albany, New York*

Jamaica Ginger Paralysis Studied 23 Years After Onset: A Clinical Report

S. Horenstein and D. J. Earl, *Boston, Massachusetts*

Cerebral Neoplasms Manifested by Psychotic or Neurotic Symptoms

Elinor R. Ives, *Los Angeles, California*

Correlative Studies of the Clinical and Laboratory Findings in 200 Head Injuries

Milton H. Kibbe, *Springfield, Massachusetts*

Muscular Dystrophy Treated with a Protein Hydrolysate and Vitamins

Francis Kruse, Jr. and A. L. Drew, Jr., *Ann Arbor, Michigan*

Wilson's Disease—Pseudosclerotic Form

Ben W. Lichtenstein and Ira Gore, *Chicago, Illinois*

Cervical Meningocele Producing Symptoms Simulating Herniated Disks in the Cervical and Lumbar Areas

Jack London, *Brooklyn, New York*

Acute Demyelinating Disease of the Central Nervous System: So-Called Acute Disseminated Encephalomyelitis and Acute Diffuse Sclerosis

Joseph A. Luhan, *Chicago, Illinois*

The Fate of Clinically Unrecognized Intracranial Meningiomas

Matthew T. Moore, *Philadelphia, Pennsylvania*

Cellular Responses to Brief Stress: With Particular Reference to the Liver and Autonomic Central Nervous System Nuclei

John I. Nurnberger and Malcolm Gordon, *Hartford, Connecticut*

Hand Prominence in Sentient Man

Alvin L. Robins and Robert Cohn, *Bethesda, Maryland*

Paper Electrophoretic Studies on Cerebrospinal Fluid and Serum Proteins in Multiple Sclerosis

Elizabeth Roboz, Walter C. Hess, Francis M. Forster, and Diana M. Temple, *Washington, D.C.*

Oxidation and Reduction Processes in the Nervous Tissue in Experimental Allergic Encephalomyelitis

Leon Roizin, *New York City*

Lumbosacral Panmeningitis

M. P. Rosenblum, *Lyons, New Jersey*

Cephalic Tetanus (Report of a Case with Recovery)

Luis P. Sanchez-Longo and N. S. Schlezinger, *Philadelphia, Pennsylvania*

Orbital Undercutting in the Aged

William B. Scoville, *Hartford, Connecticut* and V. Gerald Ryan, *Portland, Connecticut*

The Diagnostic Significance of Cerebral Muscular Atrophy in Parietal Lesions

Alex Silverstein, *Philadelphia, Pennsylvania*

Cheiralgia Paresthetica (Wartenburg's Disease)

Bertram E. Sprofkin, *Nashville, Tennessee*

Muscular Dystrophy, Further Observations on Treatment with Amino Acids, Folic Acid, and Vitamins

J. Ray Van Meter, *San Francisco, California*

Pyridostigmine (Mestinon) in the Treatment of Myasthenia Gravis

Martha R. Westerberg and Kenneth R. Magee, *Ann Arbor, Michigan*

CORRECTION

Birger R. Kaada, Jan Jansen, Jr. and Per Andersen: Stimulation of the hippocampus and medial cortical areas in unanesthetized cats, Neurology 3:844-857, 1953.

Figure 3 on page 849 should be figure 4, and figure 4 on page 851 should be figure 3.

REVIEW COURSES IN BASIC and CLINICAL NEUROLOGY

APRIL 26, 27, 28, 1954

Preceding the

1954 AMERICAN ACADEMY OF NEUROLOGY MEETING

Shoreham Hotel, Washington, D. C.

THE HYPOTHALAMIC REGION—April 26, 1954. Dr. A. L. Sahs, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROPATHOLOGY—April 26, 1954. Dr. Fae Y. Tichy, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00. Deposit on Loan Box: $25.00.

COMA—April 27, 1954. Dr. Joe R. Brown, chairman. Fees: Juniors. $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

DISEASES OF THE SPINAL CORD—April 27, 1954. Dr. Benjamin Boshes, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROPHYSIOLOGY—April 27-28, 1954. Dr. J. L. O'Leary, chairman. Fees: Juniors: $15.00; Fellows, Actives and Associates: $20.00; Non-members: $25.00.

THE REFLEXES—April 28, 1954, A.M. Dr. Russell N. DeJong, chairman. Fees: Juniors: $5.00; Fellows, Active and Associates: $8.00; Non-members: $12.00.

HEADACHE—April 28, 1954, P.M. Dr. A. P. Friedman, chairman. Fees: Juniors: $5.00; Fellows, Actives and Associates: $8.00; Non-members: $12.00.

ENROLLMENT FOR ALL COURSES IS LIMITED

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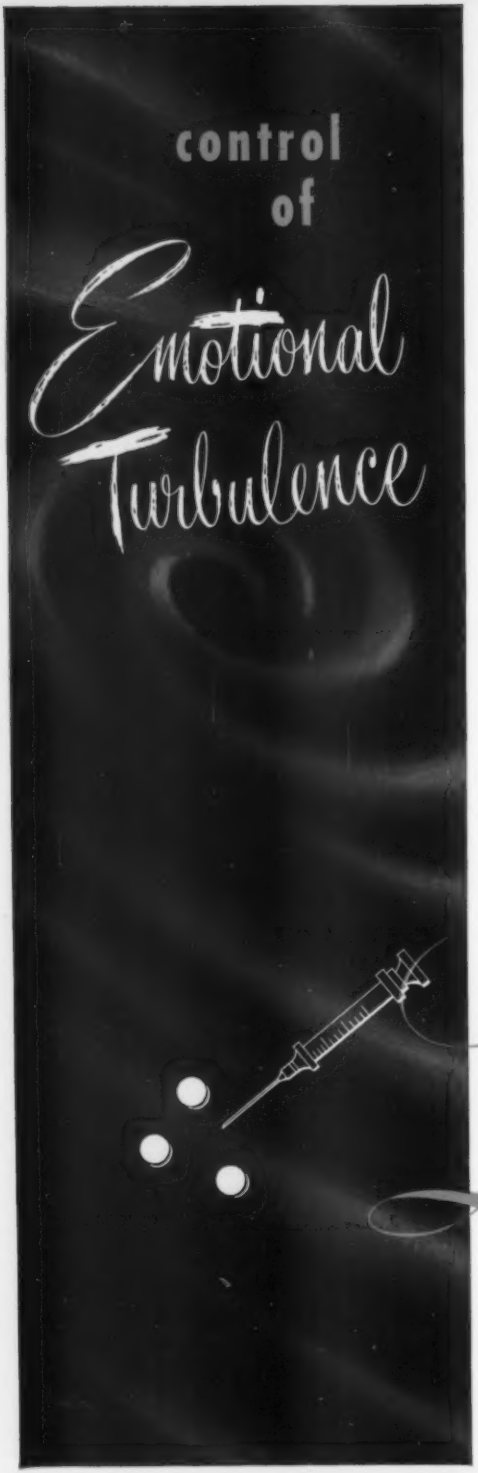

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